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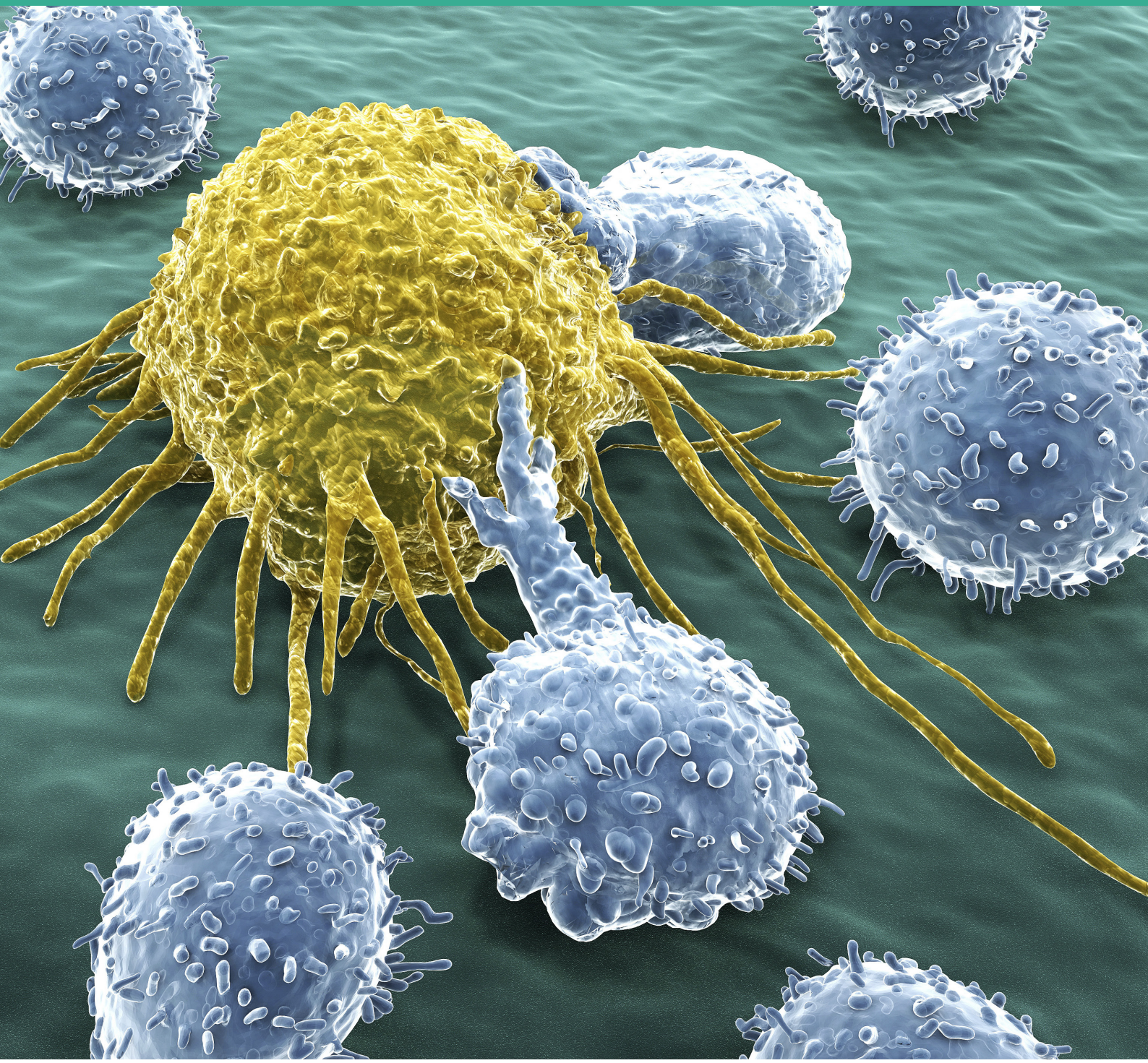

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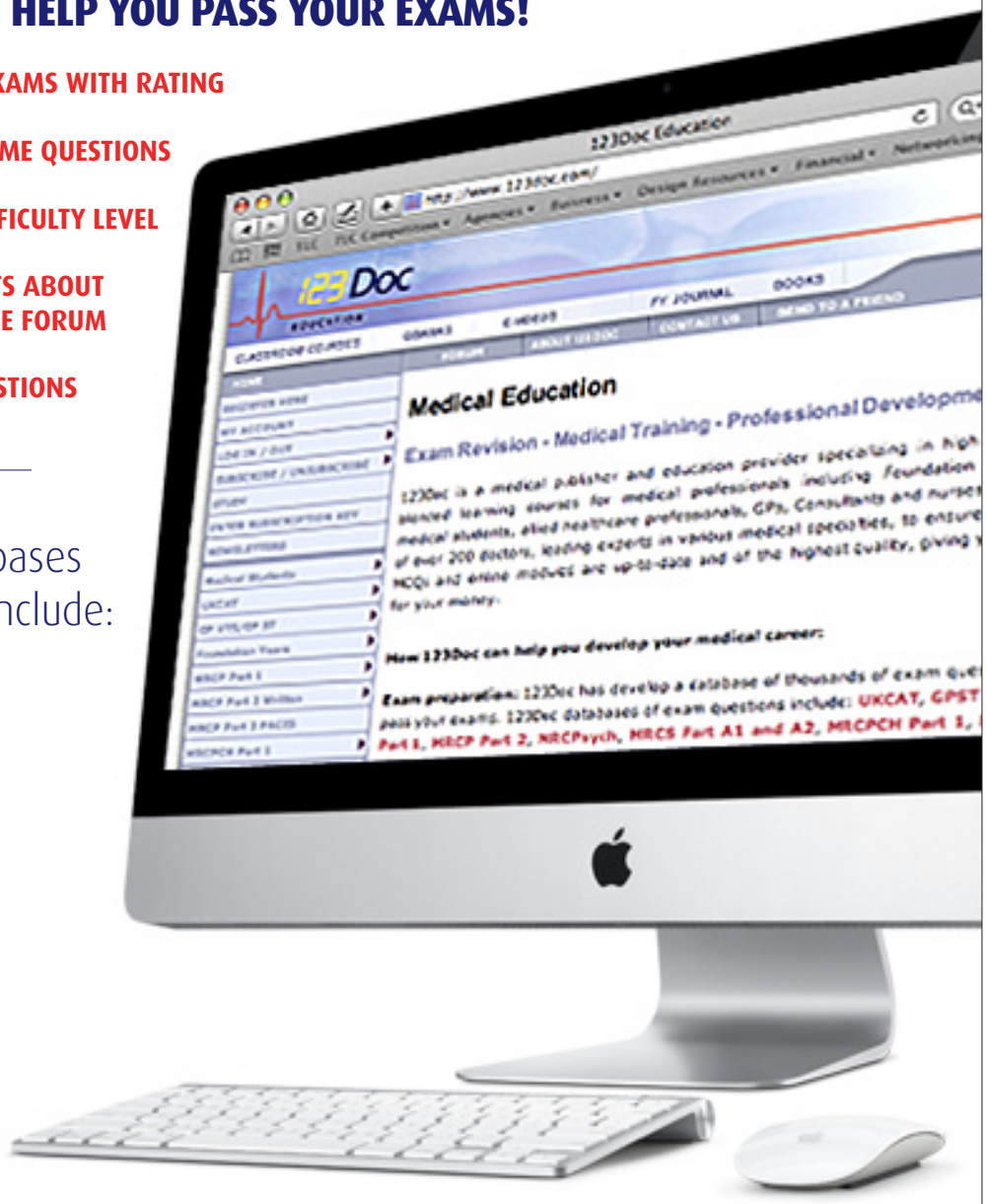

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Volume 10

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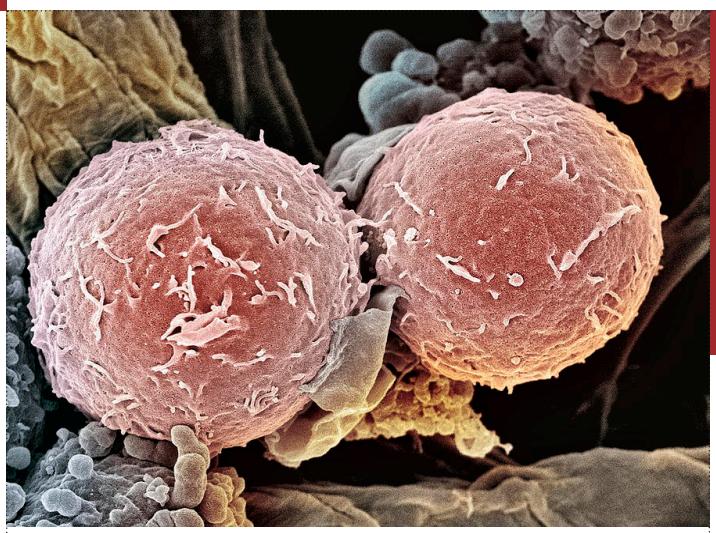
A CASE OF MEDIASTINAL GERM CELL TUMOUR & CONCURRENT ACUTE MEGAKARYOBLASTIC LEUKAEMIA

H Smith, I Hennig



Abstract

A case of a twenty year old man with a concurrent diagnosis of a mediastinal germ cell tumour and acute megakaryoblastic leukaemia. The germ cell tumour caused local compression, nearly occluding the superior vena cava. Treatment decisions were complex due to the fact that he had two synchronous rare malignancies both requiring systemic treatment, but with very few drugs treating both. A particular difficulty with this case was deciding which of the various treatment options would have first priority.

After discussion between specialists he went on to have radiotherapy to stabilise his mediastinal germ cell tumour followed by chemotherapy for his leukaemia and then a different chemotherapy regime for his germ cell tumour. He may subsequently require surgery to remove any residual germ cell tumour and a bone marrow transplant to treat the leukaemia. Also relevant to junior staff on the ward was the patient's age, as he was similar in age to the junior doctors treating him.

Case History

A twenty year old man presented to his GP with a two week history of shortness of breath on exertion and orthopnea. On respiratory examination basal crepitations could be heard on the right of his lung and there was decreased air entry over the right lung base, with associated dullness to percussion. He was referred to his local hospital where a chest x-ray showed a mediastinal mass, subsequently confirmed on CT. Based on his imaging, combined with elevated germ cell tumour markers, he was diagnosed with a mediastinal germ cell tumour and transferred to the regional tertiary centre.

A Case of Mediastinal Germ Cell Tumour & Concurrent Acute Megakaryoblastic Leukaemia
Patient Management

His past medical history includes mild asthma and previous fractures to his left ankle and left toe. He is a student, living with his parents and sister, he is a non-smoker and admitted to drinking alcohol socially. His family history includes a grandfather with prostate cancer, a great-grandfather who had cancer of the stomach, but no history of testicular cancer or testicular maldescent.

On admission to the specialist centre routine blood tests and repeat tumour markers were requested. A repeat Chest x-ray (image 1) showed a large anterior mediastinal mass with an associated right sided effusion and atelectasis. Review of the CT scan confirmed a large anterior mediastinal mass and impending superior vena cava occlusion (image 2).

A testicular ultrasound did not find any evidence of a testicular primary. He was started on Co-codamol for pain and Allopurinol to prevent hyperuricemia and gout. Hyperuricemia is one character of tumour lysis syndrome (1), which can occur with rapid cell death in haematological and some solid malignancies, such as germ cell tumours, following commencement of chemotherapy.

His admission bloods showed: beta HCG 182 (Norm: 0-2 IU/L), AFP 3560 (0-10kU/L) and LDH 3738 (220-450U/L), confirming the diagnosis of a non-seminomatous germ cell tumour. In view of the fact that he had a mediastinal primary, he fulfilled the criteria for poor prognosis disease. His FBC showed he was anaemic and thrombocytopenic, with 'abnormal looking cells, query lymphoblasts' noted on his blood film.

A blood sample was sent for peripheral blood immunophenotyping, which was CD 45, CD117, CD61, CD56 and CD7 positive, consistent with megakaryloblastic leukaemia. A bone marrow biopsy subsequently confirmed the diagnosis, showing almost complete replacement of normal bone marrow by leukaemic infiltrate. Intensive discussions ensued between the Oncology and the Haematology teams regarding the best course of treatment, and the most appropriate sequencing.

A CASE OF MEDIASTINAL GERM CELL TUMOUR & CONCURRENT ACUTE MEGAKARYOBLASTIC LEUKAEMIA

H Smith, I Hennig

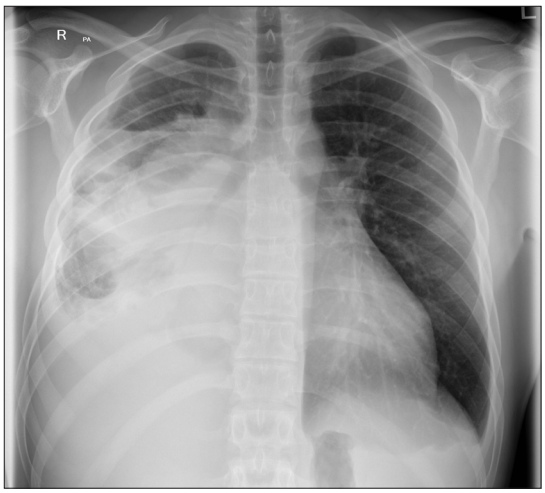


Image 1

The patient went on to have radiotherapy to his mediastinum. He received 20Gy in 5 fractions in an attempt to prevent complete superior vena cava occlusion. He then commenced induction chemotherapy for his leukaemia. He had two cycles of Cytarabine (Ara-C), Daunorubicin and Etoposide (ADE) over two months. The Etoposide, though part of the treatment for leukaemia, was expected to have some effect on the mediastinal germ cell tumour.

After the first cycle of ADE there was evidence of partial remission of his leukaemia as a repeat bone marrow aspirate showed only 1% blasts (CD61 positive) and cytogenetics were negative for gain of RUNX1. Therefore, a further cycle of ADE chemotherapy was given. Thankfully, following his radiotherapy and over the two months of his ADE treatment his germ cell tumour markers (AFP, HCG and LDH) steadily decreased (see table I) and a subsequent CT showed no progression of his germ cell tumour (image 2).

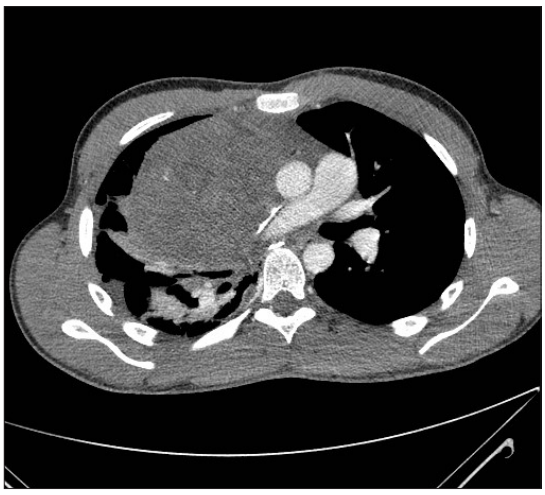


Image 2

He has recently started accelerated BEP (Bleomycin, Etoposide and Cisplatin, 4 cycles planned) with GCSF injections between cycles. This regimen was chosen for dose intensity and to minimise the interval between ADE induction chemotherapy and allogeneic bone marrow transplant required to treat his leukaemia. Accelerated BEP is given over the 8 weeks instead of the usual 12 weeks needed for standard BEP chemotherapy or 15 weeks for more intensive CBOP BEP chemotherapy. On completion of his BEP chemotherapy, surgery is planned if any significant residual mediastinal germ cell tumour remains, followed by bone marrow transplant. Thankfully, a family member was found to be a suitable match.

Tumour Marker/Date	16/09	24/09	01/10	08/10	14/10	21/10	29/10	4/11	11/11	20/11	30/11
AFP†(0-10 kU/L)	3560	3011	2364	935	464	178	50	33	13	7	5
HCG‡(0-2 IU/L)	182	198	144	30	4	<1	<1	<1	<1	<1	3
LDH§(220-450 U/L)	3738	10021	3474	635	655	478	311	305	188	633	397
	↑RT	↑ADE #1					↑ADE #2			↑BEP #1	

Table 1

†Alpha-fetoprotein, ‡ Human chorionic gonadotropin, § Lactate dehydrogenase

RT: Radiotherapy to stabilise mediastinal germ cell tumour; ADE: Cytarabine, Daunorubicin, Etoposide chemotherapy for leukaemia; BEP: Bleomycin, Etoposide, Cisplatin chemotherapy for germ cell tumour

Discussion

Mediastinal germ cell tumours account for approximately 2-5% of all germ cell tumours (2). Acute Megakaryoblastic Leukaemia accounts for 3-5% of Acute Myeloid Leukaemias (3). Both malignancies are rare in their own right; having them both simultaneously is even rarer. However, synchronous or metachronous occurrence of the two malignancies has been reported, although the proposed genetic link (isochromosome 12p) was not found in our patient (2).

Both malignancies have established treatment algorithms which have been researched in some detail. However in this case the challenge was which cancer to treat first. The mediastinal germ cell tumour was discovered first and it was only the pre-chemotherapy blood tests that documented the Acute Megakaryoblastic Leukaemia.

The standard treatment for mediastinal germ cell tumours is Bleomycin, Etoposide and Cisplatin (BEP) or Carboplatin, Bleomycin, Vincristine and Cisplatin followed by BEP (CBOB BEP) chemotherapy (4). The suggested treatment for Acute Myeloid Leukaemia is a combination of Cytarabine , Daunorubicin, Mitoxantrone, Etoposide , Fludarabine (5).

A CASE OF MEDIASTINAL GERM CELL TUMOUR & CONCURRENT ACUTE MEGAKARYOBLASTIC LEUKAEMIA

H Smith, I Hennig

In this case the patient was treated with ADE therapy, especially as Etoposide, a topoisomerase II inhibitor, has activity in both leukaemia and the germ cell tumours (6). Intensive discussions took place between the Consultant Oncologist and the Consultant Haematologist in charge of his care to the most appropriate chemotherapy regimen and sequence of treatment to best treat one malignancy without neglecting the other. Bone marrow aspirate had shown that the patient had very little bone marrow reserve as his bone marrow had almost completely been replaced by the leukaemia.

It was, therefore, not safe to start chemotherapy for his germ cell tumour first. However, there was concern that his SVCO might worsen if he received leukaemia chemotherapy first. The decision was made to buy time by treating his impending SVCO with radiotherapy to provide time for his leukaemia chemotherapy to clear his bone marrow and allow him to regain normal bone marrow activity. This in turn would allow his Oncologist to treat him with chemotherapy for the germ cell tumour.

Timing has been the key in this case. In the space of three months the patient was diagnosed with two different rare malignancies, both with significant prognostic implication, had radiotherapy, two cycles of ADE chemotherapy, and four cycles of BEP chemotherapy, and he has much more treatment to come. Either systemic intensive treatment can put a significant physical strain on the patient as well as cause significant psychological distress. Our patient has, so far, coped amazingly well with his situation. He has had to put his life on hold and spend a lot of time in hospital, which is unexpected for a young man of his twenties who should be enjoying himself with his whole life ahead of him.

For the junior medical staff on the ward, treating and supporting a patient who has been diagnosed with two life-threatening simultaneous malignancies, and who is of a similar age can be challenging psychologically. Opportunities offered by the senior medical team to allow any concerns, fears and distress to be raised is vital to support junior members of the team in these situations. Thankfully a strong support network was in place within the department provided to junior members of the team by clinical supervisors and registrar buddies.

MCQs

1.) What is the most common diagnosis for breathlessness on exertion and cough in an apyrexial young person?

a. Lung cancer
b. Asthma
c. COPD
d. Pneumonia
e. PE

2.) During haematopoesis, megakaroblasts are the stem cells for which mature cell type?

a. Neutrophil
b. Lymphocyte
c. Monocyte
d. Thrombocyte
e. Erythrocyte

3.) What is the diagnosis of a germ cell tumour normally based on?

a. Histology
b. Tumour Markers (AFP, LDH, HCG)
c. Radiology
d. Radiology and Tumour markers
e. a and d

4.) What is the most common type of Acute Myeloid Leukaemia?

a. Acute Megakaryoblastic Leukaemia
b. Acute Myelomonocytic Leukaemia
c. Acute Monocytic Leukaemia
d. Acute Myeloblastic Leukeamia
e. Acute Promyelocytic Leukeamia

5.) Which of the following is NOT a differential diagnosis for elevated AFP?

a. Hepatocellular Carcinoma
b. Testicular Cancer
c. Liver Cirrhosis
d. Spermatocele
e. Pregnancy

MCQ answers and explanations

1.) Asthma is the most common diagnosis in a young person with breathlessness on exertion and orthopnea.

Cancer is rarer in the younger person. In the great majority of cases COPD occurs in older patients who have been lifelong smokers. Heart failure is also more common in the older patient. Pneumonia is a possibility but would often present with a fever and other signs and symptoms of infection.

M. Longmore, I Wilkinson, E Davidson, A Foulkes, A Mafi. Oxford handbook of clinical medicine, eighth edition. Oxford University Press. 2010.

A CASE OF MEDIASTINAL GERM CELL TUMOUR & CONCURRENT ACUTE MEGAKARYOBLASTIC LEUKAEMIA

H Smith, I Hennig

2.) A Megakaryoblast becomes a Thrombocyte through the process of Haematopoeisis.

Medical Labarotries Portal [omepage on the Internet] Cited 27/11/15, Available from: http://www.medical-labs.net/hematopoiesis-the-formation-of-blood-cells-3078/

3.) A diagnosis of germ cell tumour is made on the basis of radiology and/or histology and tumour markers, together with the clinical picture. The diagnosis cannot be made on one investigation alone, with the exception of conclusive histology.

CancerReseachUK [homepage on the Internet]. Cited 27/11/15. Available from: http://www.cancerresearchuk.org/about-cancer/type/rare-cancers/rare-cancers-name/mediastinal-germ-cell-tumours#diagnosis

4.) Acute Myeloblastic Leukaemias make up 50% of all Acute myeloid leukaemias. CancerReseachUK [homepage on the Internet].

Cited 27/11/15. Available from: http://www.cancerresearchuk.org/about-cancer/type/aml/about/types-of-acute-myeloid-leukaemia

5.) Spermatocele would not give a high AFP. Alpha fetoprotein is a protein developed by the liver of a foetus during pregnancy. Levels decrease over time. High AFP can be seen in pregnant women. It is also a marker for testicular, ovarian, biliary, stomach, or pancreatic tumours.

Medline Plus Encyclopedia [on the internet] Cited 27/11/15. Available from: https://www.nlm.nih.gov/medlineplus/ency/article/003573.htm

Authors

Dr H Smith
FY2
Nottingham City Hospital
Hucknall Road, Nottingham, NG5 1PB

Dr I Hennig
Consulatant Oncologist
Nottingham City Hospital
Hucknall Road, Nottingham, NG5 1PB.
Ivo.hennig@nuh.nhs.uk

Corresponding Author

Dr H Smith
Holly.smith13@nhs.net

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3.) Edited by E.S. Jaffe, N.L. Harris, H. Stein and J.W. Vardiman; Published by Intl. WHO classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues; Agency for Research on Cancer IARC press 2001, pages 99 - 102.
4.) CancerReseachUK [homepage on the Internet]. Cited 27/11/15. Available from: http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/mediastinal-germ-cell-tumours.
5.) MacmillanCancerSupport [homepage on the Internet]. Cited 27/11/15. Available from: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Leukaemiaacutemyeloid/TreatingAML/Chemotherapy.aspx#DynamicJumpMenuManager_6_Anchor_1
6.) Chemocare.com [homepage on the Internet]. Cited 27/11/15. Available from: http://chemocare.com/chemotherapy/acronyms/ade.aspx

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A CASE OF METASTATIC SPINAL CORD COMPRESSION

M Noble, K Bradley

Abstract

Metastatic Spinal cord compression (MSCC) is an important diagnosis that requires early recognition. The exact incidence of MSCC in the UK is not known as there is no central recording. An audit carried out in Scotland between 1997 and 1999(1) and a published study from Canada (2), suggest the incidence may be up to 80 cases per million people every year. This equates to approximately 4000 cases each year in England and Wales. If someone is known to have a cancer then the suspicion of cord compression should be raised in anyone presenting with back pain and/or focal neurological symptoms.

Case Presentation

Mrs SG is a 47 year old lady who presented to the emergency department with collapse after her legs gave way whilst at work. This was on the background of consulting her GP complaining of worsening thoracic back pain. There had been no history of trauma.

Mrs SG had no significant past medical history and did not take any regular medications.

Mrs SG lived at home with her son who had autism and was a registered carer for him. She is a non-smoker and drinks alcohol rarely.

On initial examination, Mrs SG had a normal upper limb neurological examination but was weak bilaterally in her lower limbs with proximal power of hip flexion/extension grade 3, grade 3 knee flexion/extension and grade 3 at ankle flexion/extension. Sensation was reduced distally from the umbilicus. She was able to pass urine and open her bowels. She was also noted to have a moderate pleural effusion on the left hand side. Abdominal examination was unremarkable and there was no palpable lymphadenopathy.

A Case of Metastatic Spinal Cord Compression
Patient Management

Mrs SG was admitted under the orthopaedic team who arranged a CT scan of her chest, abdomen and pelvis and an MRI of her whole spine. The CT scan report concluded: "Adenopathy on both sides of the diaphragm with a focal lesion in the enlarged spleen. Thoracic paravertebral mass compressing the cord at T9-T11 levels."

The MRI on the same day concluded: "Infiltrative process involving T9-L1 with epidural mass, cord compression, paravertebral and thoracic cage infiltrative masses with bilateral pleural effusions, para-aortic and retrocaval lymph nodes".

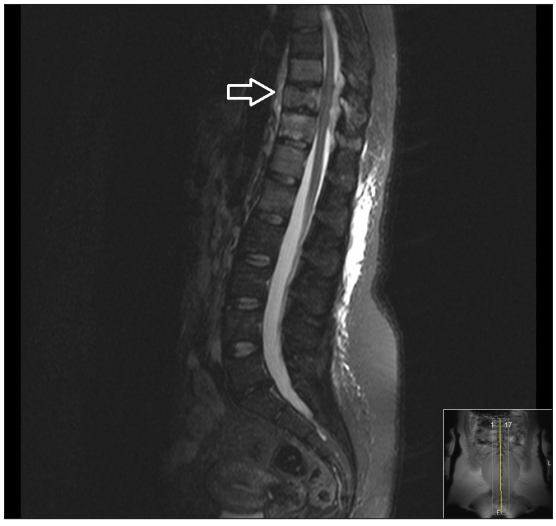

Figure 1

A referral was made to the oncology team and a biopsy of an axillary lymph node was arranged for that day followed by commencement of Dexamethasone 8mg bd. In suspected lymphoma, a biopsy is important prior to the commencement of steroids.

A CASE OF METASTATIC SPINAL CORD COMPRESSION

M Noble, K Bradley

The case was discussed with the neurosurgeons who felt there was no role for surgical intervention and emergency radiotherapy was planned. Mrs SG went on to have 5 fractions (treatments) of radiotherapy on subsequent days. Figure 2 demonstrates the Radiographer in the control room delivering treatment. Figure 3 is a Clinac© Linear Accelerator which is the machine used to deliver the radiotherapy.

Figure 2

Once the axillary node biopsy confirmed high grade lymphoma, Mrs SG commenced RCHOP chemotherapy and was scheduled for Methotrexate chemotherapy as CNS prophylaxis. With regular physiotherapy and rehabilitation, the patient was discharged a month after admission and was mobile with a Zimmer frame. She will continue to 6 cycles of RCHOP in total with curative intent.

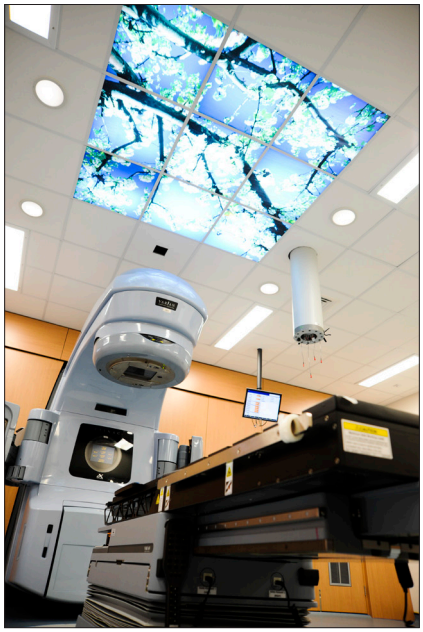

Figure 3

Discussion

Metastatic Spinal Cord compression can present in many ways. It can often be a junior doctor who first sees a patient with a history of new or worsening back pain. In this case, Mrs SG had quite marked neurological symptoms which resulted in an expedited MRI scan. As in this case, if not known to have cancer then an urgent biopsy should be obtained prior to treatment.

The use of high dose steroids with PPI cover is part of NICE guidelines (4). It is recommended that a loading dose of Dexamethasone 16 mg is used followed by a daily dose of 16 mg with food (usually in divided doses, both given no later than lunch time preferably) until surgery or radiotherapy is commenced. At this point, the steroid dose should be reduced gradually over a 5-7 day period. If at any point, neurological symptoms worsen then the dose of steroid should be reconsidered. The purpose of steroid use is to reduce oedema and thereby reduce pressure and compression of the cord. In all cases of MSCC, there should be discussion with spinal surgeons as per NICE guidelines.

Early radiotherapy is treated as a Royal College of Radiologists "category 4" (emergency). Different centres may have different protocols for radiotherapy treatment but will usually involve either a single fraction or, as in this case, 5 treatments/fractions over 5 days. Mrs SG was appropriate for radiotherapy treatment to protect the cord as she had not had tetra- or paraplegia for >24 hours. The CT planning scan allows clinical oncologists to "plan" a patient specific treatment to deliver radiotherapy within pinpoint accuracy to the target area. It also allows calculations to be made to demonstrate the doses of radiation received by other tissues as a result of the beam.

Figures 4 and 5 show the CT planning scan with the "dosimetry" applied showing where the radiotherapy is being delivered to and the different colours correspond to the "dose" or amount of radiation that area is receiving. It is usual to treat the vertebra one level above and one below the area of concern because the edge of the field (penumbra) does not deliver the full strength of the dose. For example, in the case of Mrs SG – T9-T11 was affected and so treatment was directed from T8 to T12.

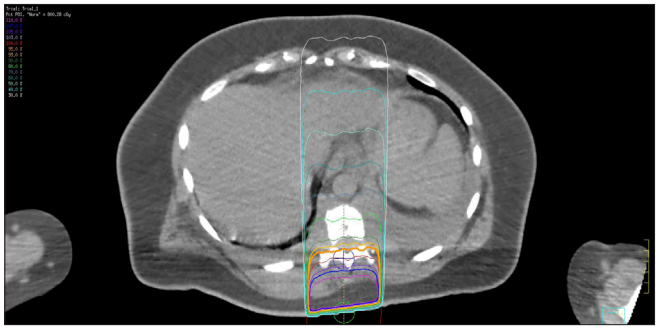

Figure 4

A CASE OF METASTATIC SPINAL CORD COMPRESSION

M Noble, K Bradley

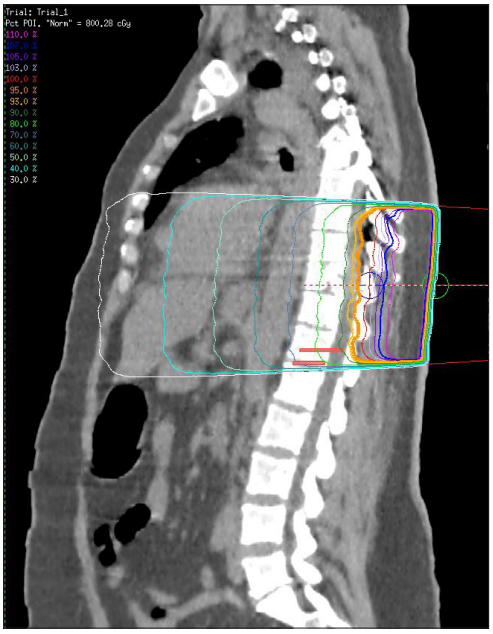

Figure 5

MCQs

1. At what level does the true cord end in an adult?

a) T12

b) L1

c) L2

d) L3

e) L5

2) As per current NICE guidelines: a patient with suspected metastatic cord compression should have investigation and treatment started within:

a) 24 hours

b) 48 hours

c) 72 hours

d) 12 hours

e) No specific time frame stated

3) In a patient who is non-ambulant secondary to paraplegia then the chances of becoming ambulant following radiotherapy is:

a) 80-90%

b) 60-70%

c) 35-45%

d) 20%

e) Less than 10%

4) A patient presenting with sensory changes distally from the nipples down and with bilateral leg weakness and urinary retention is likely to have a lesion at or around which level?

a) T2

b) T4

c) T12

d) L2

e) Multi-level

5) Which are the most common primary tumour sites to result in spinal cord compression?

a) Lung, breast, multiple myeloma, lymphoma, prostate.

b) prostate, ovarian, glioblastoma

c) Multiple myeloma, renal cell, sarcoma and lung.

d) Lymphoma, ovarian, testicular and cervical

e) Breast, renal cell, testicular and lung.

Answers

1. Answer: B:

The true cord ends at L1. Compression above this level would be cord compression and from L2 down would be cauda equina compression/ syndrome. Characteristically in cauda equina syndrome there are symptoms of urinary and faecal incontinence, sensory disturbance of the buttocks and posterior aspect of the thighs and lower motor neurone weakness localising to the myotome of the affected nerve root(s).

A CASE OF METASTATIC SPINAL CORD COMPRESSION

M Noble, K Bradley

2. Answer: A:

NICE guidelines state that treatment should be commenced within 24 hours. This therefore means that the examination, whole spine MRI, spinal assessment and discussion with spinal/surgical units need to have happened promptly to allow time for either transfer to the surgical unit or to start radiotherapy treatment.

3. Answer: E:

Local control rates for radiotherapy have been found to be in the region of 75%. This varies between tumours as some are more responsive to radiotherapy. Tumours that tend to be more radiosensitive include: lymphoma, seminoma, small cell lung cancer, breast, ovarian and prostate. Successful treatment does not necessarily mean a return to normal neurological functioning. 67-82 % of patients who are ambulant at presentation will remain ambulant with treatment.

In the non-ambulant patient secondary to para-paresis the chance of returning to ambulatory is around a third. Unfortunately for those who are non-ambulant due to paraplegia then there is a chance of 2-6% of becoming ambulant again. The chance of walking is increased if there was a more insidious onset and in those who receive treatment within 12 hours. (4)

4. Answer: T4.

The clue here is the sensory level. This is often the most useful/specific part of examination as myotomes can overlap and especially if the thoracic spine is involved. It is important to note though that the sensory level is more of a guide as it is often found that the spinal lesion may be more proximal. All segments of the spine can be affected but 70% of cases are within the thoracic spine, followed by 20% in the lumbar spine then cervical and lumbar. Thoracic pain is less common in the general population compared to the cervical and lumbar regions and so should raise suspicion of a possible malignant cause.

5. Answer: A:

In an American study looking at 15 000 hospital admission for MSCC the most common underlying diagnoses were lung cancer, breast cancer and multiple myeloma followed by both lymphomas and prostate cancer. (6)

Authors

Dr Mark Noble
Oncology SpR
Queen Alexandra Hospital
Portsmouth, PO6 3LY
mark.noble2@porthosp.nhs.uk

Katy Bradley
Clinical Oncology Consultant
Queen Alexandra Hospital
Portsmouth, PO6 3LY

Corresponding Author

Katy Bradley
Katy.Bradley@porthosp.nhs.uk

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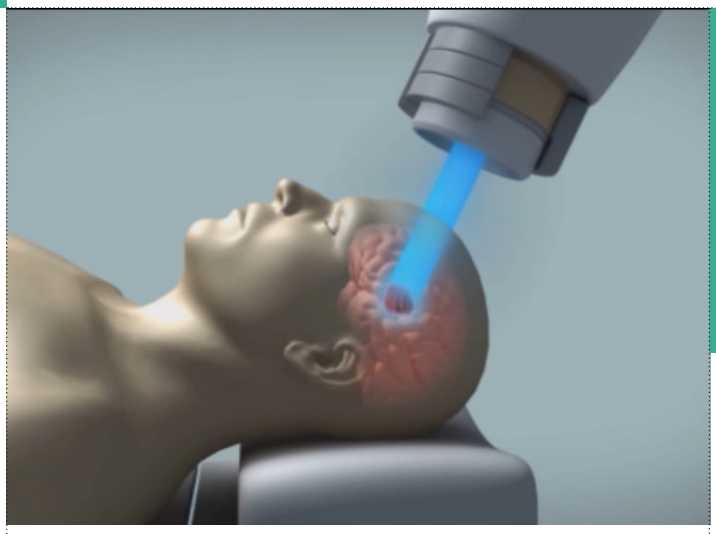
PROTON BEAM THERAPY IN CLINICAL PRACTICE

B Sanderson, A Choudhury



Abstract

For around 30 years proton beam therapy (PBT) and other forms of charged particle therapy have been used to treat solid malignancies. Currently there are many barriers to its widespread implantation in clinical practice; most crucial to this, is the current debate over its cost-effectiveness. Despite the numerous theoretical advantages conveyed by protons there has so far been little data demonstrating its superiority over photon radiotherapy with regard to improved clinical outcomes.

This review will discuss the molecular characteristics of protons and the advantages and disadvantages these properties convey. With two new national PBT centres commissioned for the UK, we will also discuss the recent evidence comparing PBT and photon radiotherapy for malignancies in which PBT has been approved and those in which evidence is lacking. PBT has recently moved into the public eye, and in a time of economic austerity the rationale and evidence for PBT is sure to be an important topic of debate.

1. Introduction

Photon radiotherapy (RT) has been used in the treatment of cancer patients almost since its discovery in 1895. Today around 50% of cancer patients receive radiotherapy in the radical, adjuvant or palliative setting (1). Theoretically, RT can control any tumour in vitro with a high enough dose of radiation; however, in vivo this is limited by the dose delivered to surrounding normal tissues and critical structures. Currently, sophisticated planning techniques are employed to minimise the dose received by normal tissues whilst allowing the dose to be escalated within the tumour.

This involves comprehensive clinical, surgical and radiological assessment to identify the tumour and the tissues which are macroscopically involved (gross tumour volume; GTV). Next, a volume containing potential subclinical disease must be identified (clinical target volume; CTV). Finally, in order to account for tumour movement during radiotherapy a larger planning target volume (PTV) is calculated (Figure 1) (2). Since accounting for both subclinical disease and movement means some normal tissue irradiation, patients can suffer from adverse effects of RT.

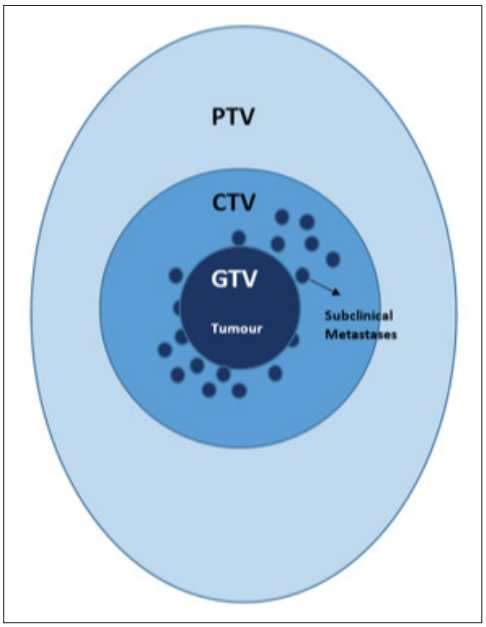


Figure 1: Radiotherapy treatment volumes. Gross tumour volume (GTV) is macroscopic disease detected by clinical, operational and radiological examination.

Clinical target volume (CTV) is the volume to cover potential subclinical disease. Planning target volume (PTV) is the CTV plus an added margin to allow for tumour movement during treatment. Adapted from (2).

In 1946 protons were proposed as an attractive alternative and potentially superior modality of RT due to superior dose-depth distributions thereby allowing dose escalation within the target volume whilst limiting the dose received by normal tissues (3). The first patients were treated in adapted university physics laboratories and since then numerous dedicated facilities have become operational. As of March 2013 over 93,000 patients had received all or part of their RT via protons (4).

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Currently, no high-energy proton beam therapy (PBT) centres exist in the UK. In 2009, the National Radiotherapy Advisor Group (NRAG) determined an immediate need for up to 400 high priority patients per year to have access to PBT. In order to accommodate this, patients are referred to overseas facilities at great cost to the NHS. Between 2008- 2012, 160 patients had completed their PBT, of which 107 were children.

The number of patients referred to-date has been less than expected; however, this is expected to escalate as experience grows (5). In the last decade the use of PBT has increased and now, with two new high-energy national PBT centres on the horizon in the UK, the technology is moving into the public eye with a high amount of media and patient attention. PBT has been described as the world's most costly medical device and in the current economic climate with a paucity of hard evidence demonstrating and quantifying its superiority over photon RT some are questioning whether it is a sensible and sustainable investment (6).

2. The promise of protons

Radiation exerts its effect through direct (direct double-stranded DNA breaks) and indirect (free-radical generation) damage. Tumour cells have a reduced ability to repair DNA damage compared to normal tissue. Protons are more densely ionising than photons and therefore exert the majority of their effect through double-strand DNA breaks which are inherently more difficult for cells to repair (Figure 2).

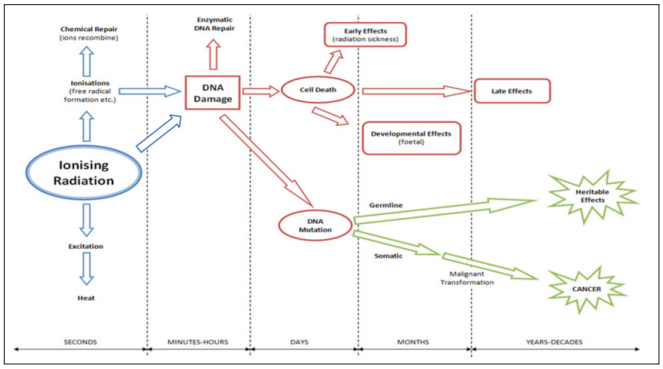

Figure 2: The classic paradigm of radiation injury. Adapted from (7).

The physical properties of protons have long been recognised as being theoretically superior to photons. These heavier, charged ions deposit the majority of the dose at the end of their path. This sharp loss of energy within the last few millimetres of penetration is known as the Bragg peak and can be altered by increasing or decreasing the beam energy. In addition, the entrance dose is significantly reduced (around 30% of the maximal dose) whilst the distal dose is practically zero.

In contrast, photons deposit the majority of their dose at the entrance region with an exponential decrease in dose with increasing tissue depth (figure 3a). As a result, protons have approximately a 60% reduction in the integral dose (the total energy absorbed by the body, it is the product of the total volume of tissue irradiated and the total absorbed dose) (8).

In addition to the Bragg peak properties, protons also have a very sharp penumbra (the rapidity of dose fall-off at the lateral edges of the beam) at shallow-moderate depths (9). The Bragg peak properties in addition to the sharp beam penumbra results in the potential for extremely accurate dose-depth distributions and target volume conformation.

Consequentially, there is a theoretical capability for significant dose escalation within the target volume whilst limiting the dose received by adjacent critical structures which is generally a dose-limiting factor (figure 3d & e). This is of particular importance in paediatric patients as children are more susceptible to the normal tissue effects of RT, particularly growth and function for example, risks of learning difficulties, cognitive dysfunction and growth and hormonal abnormalities in children having brain RT. Patients who live longer are at greater risk of developing secondary malignancies as a result of RT (10).

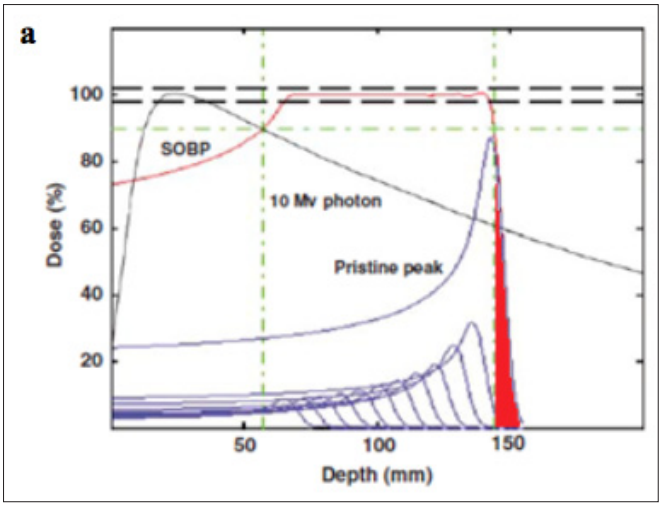

Figure 3a. Depth-dose distributions for a spread out Bragg peak (red line), its constituent pristine Bragg peaks (blue) and the location of the penumbra (red area under the curve). Also shown is the equivalent depth-dose distribution for a photon beam (black). Target depth (tumour) is marked by green dashed lines. Taken from (11).

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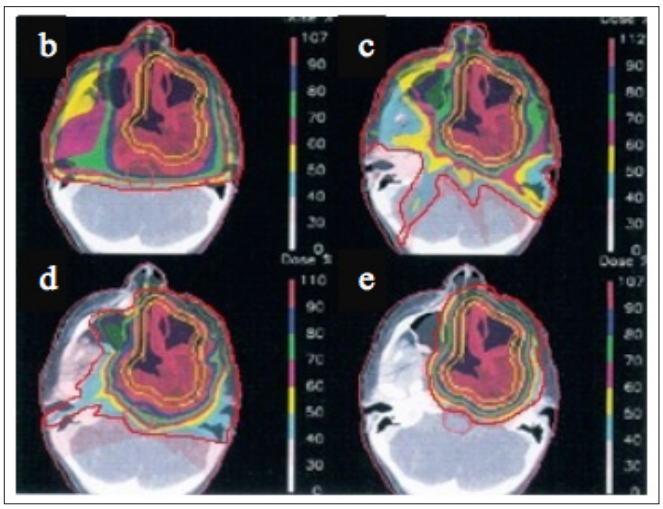

Figure 3b-e: Dose distributions for a patient with rhabdomyosarcoma. Note that the doses superficial and deep to the tumour are higher in photon therapy. Comparative dose distributions for (b) conventional photons (c) IMRT (d) spot-scanned protons and (e) intensity-modulated protons. Marked in red at the periphery of the dose distributions is the location of the lateral edge of the penumbra. As you can see, this is much closer to the target volume for proton therapy. Adapted from (12).

Despite the theoretical advantages, there are several potential issues which need careful consideration to ensure clinical outcomes are not compromised. First, at tissue depth >10cm the stopping distance (i.e. the precise location of the Bragg peak) becomes blurred, this is known as the "end-of-range-uncertainty". Similarly, at greater depths there is considerable lateral scattering producing a substantial penumbra resulting in a loss of lateral margin definition. In order to compensate for this, beams are often planned to overshoot the tumour to ensure adequate coverage (4).

These issues result in an increased dose to the surrounding normal tissues, negating the positive physical characteristics of protons. Second, protons are highly susceptible to tissue inhomogeneity (significantly more so than photons). Any changes to the tissues in the treatment plan brought about by imperfect positioning of the patient or inevitable organ movement can affect the dose delivered to the target volume and the surrounding normal tissue (13). Third, the relative biological effectiveness (RBE; the ratio of photon and proton dose producing the same biological effect) has been measured as 1.1 meaning normal tissues respond similarly to protons as to photons. However, just beyond the Bragg peak, the RBE may be higher than anticipated (around 1.6).

At lower doses this is not significant; however, when giving high doses like 80Gy, small differences in the RBE can be critical (4). Moreover, today the predominant method of proton delivery is passive scattering. A by-product of this method are neutrons in the head of the PBT machine. The incidental exposure of patients to neutrons may actually lead to an increase in secondary malignancy (14). Despite these limitations, it should be noted that advances in planning techniques and PBT technology, such as image-guided delivery systems, have already begun to ameliorate these issues.

3. Current clinical evidence

Although the theoretical benefits of PBT are well documented, there is a paucity of data supporting its use over conventional RT to treat most malignancies. Data is starting to emerge showing a benefit for PBT in certain rare malignancies such as ocular and skull-base tumours and certain paediatric tumours; however, the majority of PBT delivered in the world is to prostate cancer, an indication with no clear advantage over photon RT. The reason for this is related to cost. Proton beam centres are very expensive and prostate cancer patients are quick to treat, have relatively good outcomes and come in large numbers.

In the UK, the philosophy behind the national proton centres will be to treat patients who may gain clinical benefit from proton treatment rather than a pure economic rationale. In some countries with a mixed market healthcare economy, in order to make the technology a viable investment the treatment of more common malignancies is required. The ethics of treating cancers where there is little potential clinical advantage such as prostate cancer are questionable. To try and resolve this question in prostate cancer, there is currently a randomised clinical trial recruiting in the US comparing prostate cancer photon vs proton radiotherapy.

3.a) Paediatric Tumours

The use of RT to treat malignancies of childhood has two main issues: first, a higher risk of secondary malignancy 10-15 years later and second, an increased risk of normal tissue toxicity and morbidity (8). Data is now emerging showing that the theoretical benefits of PBT are translating into real improvements in clinical outcomes for these patients (12). Tumours with the greatest potential benefit of PBT are those which are adjacent to critical structures or those in which dose escalation is limited by normal tissue toxicity. As such, tumours of the CNS, head and neck and eye would potentially benefit from PBT.

Rhamdomyosarcoma is the most common soft tissue sarcoma in children and is a highly malignant, locally invasive cancer, commonly arising in the head and neck. Because of the anatomical locations of many rhabdomysomarcomas and their adjacent critical structures, they are often difficult to treat surgically or with RT. Many parameningeal rhabdomyosarcoma patients treated with radiotherapy will suffer adverse effects of their treatment including endocrine deficits, facial hypoplasia, hearing loss, visual complications, neurocognitive dysfunction and secondary malignancy (16).

PROTON BEAM THERAPY IN CLINICAL PRACTICE

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Dosimetry studies have demonstrated that when compared to photon intensity modulated radiotherapy (IMRT), proton radiotherapy delivers a significantly lower dose to critical structures such as the cochlea, optic nerve, parotid gland and retina (17). Clinical data for parameningeal rhabdomyosarcoma has shown significantly reduced rates of acute and late toxicity and comparable rates of disease control compared to historical patients treated with photon radiotherapy.

In orbital rhabdomyosarcoma, similar data has been published demonstrating significantly improved functional outcomes and similar disease control rates to historical photon-treated patients (18). Importantly, most of the published studies had very few patients and were somewhat underpowered. Furthermore, there are no randomised controlled trials directly comparing photon and proton radiotherapy in rhabsomyosarcoma making it difficult to draw any firm conclusions.

Similarly in medulloblastoma (19), ependymoma (20), craniopharyngioma (21), optic pathway glioma (22) and retinoblastoma (23) dosimetric and clinical studies have suggested PBT confers improved acute and long-term toxicity and a reduction in the rates of secondary malignancy. However, these studies suffer the same methodological concerns as those for rhabdomyosarcoma – too few patients and a paucity of published randomised controlled trials.

3.b) Adult Tumours

The potential benefit for PBT in adults is not the same as for children. Whilst the dose-distributions remain superior, adult tissues are no longer developing and there cannot suffer from the same developmental adverse effects of RT. Due to the significant cost of PBT, improved dosimetry alone is not enough to justify its choice as a primary treatment option for every malignancy (8). Clear evidence of superior clinical outcomes must be demonstrated before PBT can be recommended over photon RT. In adults, the evidence suggests PBT should be recommended for certain chordoma, chondrosarcoma and uveal melanoma patients; however, 80% of the PBT delivered in the US is to the prostate (4).

Whilst PBT has the potential for dose-escalation in prostate cancer, current IMRT technology can safely deliver doses as high or even higher than can be delivered with PBT (24). The reason for this is the depth at which the prostate sits and the inhomogeneity of the surrounding tissues. As discussed previously, at greater tissue depths the end-of-range-uncertainty combined with the loss of the sharp lateral penumbra results in similar rates of toxicity. Due to the end-of-range-uncertainty lateral proton beams must be utilised.

This means the proton beam must take the longest possible route to the target tissue and also results in a significantly higher dose in the femoral neck, potentially increasing the risk of fractured neck of femur. Konski et al. has demonstrated through modelling studies that dose escalation to 92Gy may confer a 10% improvement in five year freedom from biochemical failure in intermediate risk patients (25).

However, the five year biochemical progression free survival for intermediate risk patients is already at 90% from data presented earlier this year with doses less than 92Gy (26). The probability of cost effectiveness reaches 50% if the patient lives for 15 years beyond treatment. In younger patients this may fall within the currently accepted standards of economic viability ($50,000/£30,000 per QALY).

However, several issues are present within this study. First, intermediate risk prostate cancer represents only 15-20% of all prostate cancer cases. Second, most intermediate risk prostate cancer patients are elderly and are likely to have co-morbidities and an already limited life expectancy. Third, younger patients are more likely to be eligible for other methods of treatment such as RT, brachytherapy and surgery which are already significantly cheaper than PBT. Finally, dose escalation to 92Gy is as yet unheard of. Currently protocols for PBT treatment to 82Gy are being developed in some hospitals in the US (27).

In contrast, in malignancies which are close to adjacent critical structures and normal tissues such as uveal melanoma, chordoma and chrondrosarcoma PBT has several benefits. Uveal melanoma is the most common primary intraocular malignancy in adults. Recent studies have shown improved local control with PBT compared to brachytherapy, but no significant difference in rates of mortality or surgical enucleation (28). Chordomas and chondrosarcomas are locally aggressive primary bone tumours which arise in the skull base and spine and the pelvis, femur and scapula respectively.

Complete surgical resection is often extremely difficult, and acceptable rates of local control are often impossible without RT as an adjunct or alternative. Due to the constraints of adjacent critical structures and normal tissue, dose escalation with conventional RT is impossible. Reviews of historical results demonstrate superior local control rates compared to IMRT and stereotactic RT (29); however, it is important to note that the origin of much of this data was from single-institution series and will have almost certainly been subject to some selection bias. Regardless, protons and other particle therapies have been established as the standard of care for these rare cases.

For other common malignancies such as breast, lung, brain, head and neck and gastrointestinal cancers proton therapy may have a role in providing a safe method of dose escalation whilst sparing normal tissues. However, as yet there is no clinical data to suggest that PBT offers any benefit over conventional photon RT delivery systems such as IMRT and stereotactic RT (8).

In 2013, the UK government confirmed plans to develop two national high-energy PBT centres by 2018 – one at The Christie in Manchester and one at University College Hospital in London. There are also plans to build a research-focussed PBT centre at Oxford University (30). When operational, the centres will begin to treat patients for whom current evidence already recommends PBT (Table 1), although there is ongoing consideration for the expansion of this list based on the published evidence.

PROTON BEAM THERAPY IN CLINICAL PRACTICE

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Adult	
	Base of skull and spinal chordoma
	Base of skull chondrosarcoma
	Spinal and paraspinal bone and soft tissue sarcomas (Non-Ewing's)
Paediatric	
	Base of skull and spinal chordoma
	Base of skull chondrosarcoma
	Spinal and paraspinal 'adult type' bone and soft tissue sarcomas
	Rhabdomyosarcoma
	Orbit
	Parameningeal and head and neck
	Pelvis
	Ependymoma
	Ewing's sarcoma
	Retinoblastoma
	Pelvic sarcoma
	Optic pathway and other selected low grade glioma
	Craniopharyngioma
	Pineal parenchymal tumours (not pineoblastoma)
	Esthesioneuroblastoma

Table 1: List of approved diagnoses for referral for PBT in the UK base of current evidence. Adapted from (30).

4. Future developments

The advent of IMRT has substantially reduced the difference between proton and photon plans. It is clear that as clinical experience with PBT increases, so will the drive to improve the technology. The development of intensity-modulated proton therapy (IMPT) may do for protons what IMRT did for photons, once again separating proton and photon treatment plans. Institutes are now starting to implement IMPT and create protocols for its use; however, whether this will result in a drastic improvement in clinical outcomes is unknown.

Currently, PBT is amongst the most expensive of medical technologies. This reduces its availability and therefore its research and development potential. If facilities were more affordable, the price gap between proton and photon treatment would close allowing the more widespread implementation of PBT. Other authors have suggested a time when radiotherapy centres use a combination of different beams of various properties, taking a step towards personalised radiotherapy (8).

Finally, we must acknowledge that further evidence is required in order support the widespread use of PBT. In certain malignancies (e.g. paediatric rhabdomyosarcoma) it could be seen as unethical to subject children to modalities of radiotherapy which are obviously inferior. Similarly, in cancers for which PBT will obviously serve no role (e.g. skin cancer) there is no need for randomised controlled trials (RCTs). However, in cancers which currently occupy somewhat of a PBT grey area (e.g. prostate) RCTs will be essential for providing a solid evidence base either for or against its use.

Multiple Choice Questions

1. The most radiosensitive phase of the cell cycle is...

A. S

B. G1

C. G2

D. G2-M

E. 0

2. How does proton beam therapy inflict damage?

A. It causes formation of pyrimidine dimers

B. It causes free radical general

C. It induces DNA strange damage through thermal injury

D. It causes linear acceleration injury

E. It damages DNA repair mechanisms leading to mitotic catastrophe

3. What is the most significant adverse effect of radiotherapy in children?

A. Secondary malignancy

B. Growth retardation

C. Learning difficulties

D. Cataracts

E. Early/Late puberty

PROTON BEAM THERAPY IN CLINICAL PRACTICE

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4. Which characteristics make protons so effective in paediatric malignancy?

A. They exert the majority of their effect by the direct DNA damage pathway

B. They do not scatter much within tissues

C. They have a relative biological equivalent to photons of 1.1

D. They deposit the vast majority of their dose at a designated depth with zero exit dose

E. They are able to specifically target tumour cells, leaving normal tissue undamaged

5. What is the main perceived barrier to proton beam therapy in the UK?

A. Less effective than photon therapy

B. Significantly higher cost than photons

C. Unethical for clinical trials

D. Lack of evidence for its use in clinical practice compared to photons

E. Not enough patient demand to make it a viable treatment option

Answers

1. D

Studies have demonstrated increased radiosensitivity during G2-M phase of the cell cycle. As tumours typically demonstrate uncontrolled growth and proliferation they have a higher proportion of cells in this radiosensitive stage in the cell cycle compared to normal tissue. This, in combination with their inability to repair DNA damage to the same degree as normal tissue forms the basis of using radiotherapy to treat malignancies.

2. C

Whilst protons do cause free radical generation, due to their extremely high mass (x1000 that of an electron) and positive charge they are more likely to induce direct DNA single- and double-strand breaks through thermal injury. And whilst this results in mitotic catastrophe, the effect is not to damage the DNA repair mechanisms, but DNA itself. Answers A and D are simply incorrect.

3. A

Whilst all answers are late effects of radiotherapy; one can argue that secondary malignancy is the most severe. Some may view this as a reason to avoid radiotherapy in children altogether; however, one must remember that these children already have malignancy and without radiotherapy would have a significantly reduced life expectancy. Secondary malignancy as a result of radiotherapy generally manifest 10-15 later after treatment. Children are around 10 times more sensitive to radiotherapy-induced secondary malignancy and at 20 year follow-up around 20% of deaths are due to secondary malignancy.

4. D

The ability of protons to be able to deposit almost all of their dose within the tumour and no dose distal means that protons have the potential for vastly superior dose conformation thereby significantly reducing the dose to normal tissues. E is incorrect, protons cannot autonomously target tumour cells. Whilst A, B and C are true, this is not the reason why their advent into clinical practice is exciting.

5. B

This may be somewhat of a trick question. It is known that a significant barrier to PBT is its astronomical cost. As it stands, PBT is the single most expensive medical treatment device in the world. As a clinician you may be tempted to choose C or D; however, realistically it is the cost that is the main obstruction. A is incorrect because it is as effected as photon therapy in many cases and as we have discussed better for paediatric CNS malignancy.

Authors

Dr Benjamin Sanderson MBChB, MRes
The Christie NHS Foundation Trust
Manchester
M20 4BX

Department of Clinical Oncology
The Christie NHS Foundation Trust
Wilmslow Road
Manchester
UK, M20 4BX

Dr Ananya Choudhury MA, PhD, MRCP, FRCR
The University of Manchester
Manchester Academic Health Science Centre
The Christie NHS Foundation Trust
Wilmslow Road
Manchester
UK, M20 4BX

PROTON BEAM THERAPY IN CLINICAL PRACTICE

B Sanderson, A Choudhury

Corresponding Author

Dr Benjamin Sanderson
e-mail: Benjamin.sanderson@nhs.net

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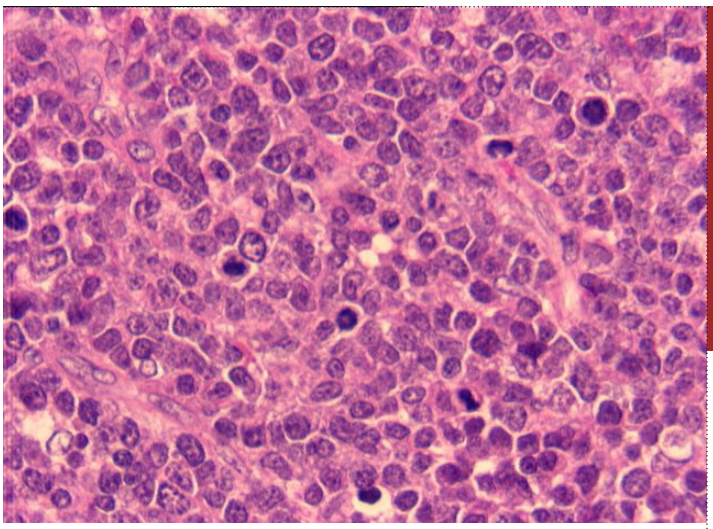
MANAGEMENT OF DIFFUSE LARGE B CELL LYMPHOMA IN THE ACUTE SETTING

A O'Callaghan, A Paschalis



Abstract

Non-Hodgkin's Lymphoma (NHL) represents a heterogeneous group of lymphoproliferative malignancies and can present in a variety of ways that can be challenging for foundation doctors in the acute setting. This case based discussion focuses on Diffuse Large B Cell lymphoma (DLBCL), an aggressive form of NHL, to highlight some of these challenges and facilitate discussion as to the management of acutely ill patients with lymphoma. Key learning points include that DLBCL is a potentially curable cancer, and the use of steroids should be avoided if possible until after a diagnostic biopsy is obtained, as steroids can be detrimental to the histological diagnostic yield.

Case History

A 73 year old man presented to the surgical assessment unit having been referred by his general practitioner with acute abdominal pain. He reported a three week history of worsening left-sided abdominal pain and fullness associated with three kilogram weight loss, night sweats and breathlessness on exertion.

He was previously fit with no co-morbidities or regular medications and had a twenty pack-year smoking history. On examination he was diaphoretic and tachypnoeic with reduced air entry at the left base on auscultation of the chest with dullness to percussion. On abdominal examination, he was tender in the left upper quadrant with a palpable large mass. He had no peripheral lymphadenopathy.

Full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs) and clotting were normal, however lactate dehydrogenase (LDH) was elevated, at 1726(> 4x normal). A Chest X-Ray confirmed a moderate left pleural effusion. CT imaging of his chest demonstrated a large left pleural effusion with pleural thickening and mediastinal lymphadenopathy, while abdominal scans revealed a 14.5 x 14.5 x 21cm soft tissue retroperitoneal mass encasing the renal vessels and displacing the left kidney forwards, as well as involving the left psoas muscle (Figure 1A). These radiological findings were suggestive of lymphoma, however sarcoma was also considered in the differential.

Management of Diffuse Large B Cell Lymphoma In The Acute Setting
Patient Management

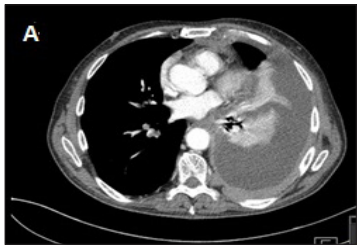


Figure 1A: Moderate left pleural effusion.

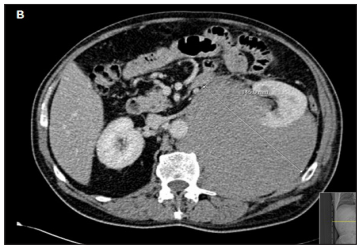


Figure 1B: Large intra-abdominal mass involving renal vessels and left Psoas muscle.

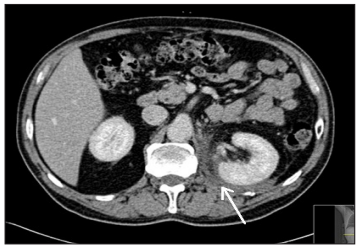


Figure 1B: Very good response to treatment with small volume of residual lymphadenopathy (arrow).

Subsequently a biopsy was obtained for histological diagnosis. As the patient was compromised by his large pleural effusion, a video assisted thoracopic surgery (VATS) was urgently arranged for symptomatic pleural drainage and simultaneous pleural biopsy. After this procedure he was commenced on Prednisolone 50mg and Allopurinol 300mg daily, once it was confirmed that the biopsy tissue would be diagnostic.

Over the next week the patient's symptoms improved and histology from the pleural tissue confirmed a diagnosis of NHL, diffuse large B cell (DLBCL) type. His disease stage was advanced (IV B) and International Prognostic Index (IPI) risk was high. He commenced R-CHOP immuno-chemotherapy. He was discharged from hospital two days after his first cycle of chemotherapy and on review three weeks later he was feeling very well, reported no pain or breathlessness and was back playing golf. He subsequently completed his treatment and achieved remission (Figure 1b), and provided this continues to be the case after 5 years follow-up, he could be considered cured.

MANAGEMENT OF DIFFUSE LARGE B CELL LYMPHOMA IN THE ACUTE SETTING

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Discussion

Presentation and Differential Diagnosis

NHLs are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behaviour(1). The incidence of NHL has nearly doubled over the last several decades as a result of improved diagnostic techniques as well as increased life expectancy(2). DLBCL is the most common sub-type of NHL with an incidence of approximately 7 per 100,000(3). However, diagnosis can be difficult, and clinical suspicion needs to be high so as not to miss important symptoms and signs.

NHL originates in lymphoid tissues but involves extra-nodal sites in up to 40% of cases and may present as a mass anywhere in the body (4). Patients with DLBCL NHL may present with palpable enlarging nodal masses, or symptoms due to disease in their chest or abdomen. Intra-abdominal involvement is very common and is an important differential to remember when reviewing a patient with abdominal pain, especially with an underlying mass (Table 1) (5).

Right Upper Quadrant	
Tender	Liver in Hepatitis
	Congestive Heart Failure
	Gallbladder in Cholecystitis
	Subphrenic Abscess
	Perinephric Abscess
	Colonic Tumour
	Abdominal Wall Haematoma
Non-Tender	Hepatomegally
	Renal Tumour
	Gallbladder
	Faecal Impaction
Right lower Quadrant	
Tender	Appendiceal Abscess
	Psoas Abscess
	Regional ileitis
	Intussusception
Non-Tender	Carcinoma of Colon
	Ovarian Tumour
Epigastrium	Hernia
	Pancreatic Tumour/Cyst
	Gastric Carcinoma
	Gastrointestinal Stromal Tumour (GIST)
	Pyloric Stenosis
	Aortic Aneurysm
	Hepatomegally
	Retroperitoneal Sarcoma
Left Upper Quadrant	Splenomegally
	Haematoma
	Pancreatic Tumour/Cyst
	Colonic Tumour
	Renal Tumour or Enlargement
	Faecal Impaction
Left Lower Quadrant	Sigmoid Diverticulitis
	Carcinoma of Colon
	Ovarian Tumour
Suprapubic	Bladder
	Gravid Uterus
	Uterine Fibroid
	Regional ileitis

Table 1: Differential Diagnosis for Abdominal Mass by Quadrant (5)

Intra-abdominal disease bulk may cause compression of the intestines giving obstructive type symptoms, obstruction of ureters leading to hydronephrosis and venous compression causing swelling of lower limbs, thrombosis or ascites. Compression of vessels (e.g. superior vena cava obstruction), airways (e.g. tracheo-bronchial compression) and nerves (e.g. spinal cord compression) requires urgent attention.

DLBCL can involve the liver, kidneys, lungs, and central nervous system mimicking presentation of commoner cancers of these sites.

A proportion of patients will have 'B symptoms' defined as fever, night sweats and weight loss.

Investigations

The aim of further investigations should be to confirm diagnosis and facilitate disease risk stratification to guide treatment (Table 2 & 3) (6). Biopsy of the most appropriate site that will yield adequate diagnostic tissue should be undertaken as a matter of urgency.

Blood	FBC, U&Es, LFTs, Clotting, LDH, Urate, Immunoglobulins, Serum Electrophoresis, Viral Screen (HIV, Hepatitis, CMV, EBV), B2-globulin
Radiology	CXR and Abdominal Plain film CT Chest/Abdomen/Pelvis +/- PET
Histology	Tissue biopsy of involved lymph node or extra-nodal site Bone marrow biopsy

Table 2: Summary of investigations for DLBCL.

1. Age > 60 years
2. Elevated serum lactate dehydrogenase (LDH)
3. Performance status 2–4
4. Stage III or IV disease
5. 2 or more extra-nodal sites involved

Table 3: The International Prognostic Index (IPI) for diffuse large cell lymphoma identifies five significant risk factors prognostic of worse overall survival (6):

Blood work includes FBC, U&Es, LFTs, and clotting to identify organ dysfunction. LDH and urate are used as surrogate markers to characterise the aggressiveness of a lymphoma and the risk of tumour lysis syndrome (TLS). TLS is the combination of hyperkalaemia, hyperphosphataemia, hypocalcaemia and hyperuricaemia that results from the release of intracellular material as the lymphoma is treated and broken down.

Aggressive lymphomas with bulky disease carry a high risk of TLS and can result in acute kidney injury, seizures and arrhythmias. Screening for HIV and Hepatitis B is recommended as both have implications for additional anti-viral treatments alongside immuno-chemotherapy.

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Radiology is fundamental to staging with CT chest, abdomen and pelvis +/- neck. Positron emission tomography (PET) is also becoming increasingly available and is the standard of care for high grade lymphoma at some centres.

Bone marrow biopsy is performed to assess if there is bone marrow involvement. All these results are then amalgamated to provide diagnosis, stage and prognostic index on which treatment decisions are based (Table 4 & 5) (7, 8).

Stage I	One group of lymph nodes is affected
Stage II	Two or more groups of lymph nodes are affected on one side of the diaphragm
Stage III	Lymph nodes are affected on both sides of the diaphragm
Stage IV	Lymphoma can be found in organs outside the lymphatic system or in the bone marrow

Table 4: Staging system for DLBCL (7)

Risk group	IPI score	Percentage of patients	5-year OS	Complete response rate
Low	0-1	35%	73%	87%
Intermediate (Low)	2	27%	51%	67%
Intermediate (High)	3	22%	43%	55%
High	4-5	16%	26%	44%

Table 5: Response Rate and Overall Survival in DLBCL Based on IPI Score (8)

Treatment and follow-up

The mainstay of treatment for DLBCL is immuno-chemotherapy, which can only be started once there is histological confirmation of the diagnosis. For this reason there is often a lag between presentation and the start of chemotherapy. In the acute setting, treatment therefore involves arranging urgent biopsy, management of symptoms such as pleural drainage for pleural effusions, correcting electrolyte imbalances and analgesia. Early referral to lymphoma team is essential. Chemotherapy can only be administered by specially trained nurses, usually on designated wards.

Steroids form part of the chemotherapy regime for DLBCL and can be initiated whilst results are awaited, particularly if patients are symptomatic or present with life-threatening complications. Prednisolone 50-100mg daily, or dexamethasone if an intravenous preparation required, is prescribed with a proton-pump inhibitor for gastric protection. It is important to note however, that steroids can degrade the quality of sampled tissue, reducing the diagnostic yield of biopsies. Therefore, where possible, steroids should not be started until one has confirmation that the biopsied tissue is sufficient for analysis.

Allopurinol 300mg daily is given to patients to enhance urate excretion and reduce the risk of TLS. However, in high risk cases Rasburicase, a recombinant version of the enzyme urate oxidase, is indicated.

R-CHOP is the first line therapy for DLBCL(9). This consists of Rituximab, a monoclonal antibody that targets the CD20 cell surface protein expressed on B lymphocytes, as well as Cyclophosphamide, Doxorubicin and Vincristine, cytotoxic agents administered intravenously. R-CHOP is usually given on an outpatient, day case, basis but acutely presenting patients with significant symptoms and systemic upset are often given their first cycle as an inpatient to facilitate ongoing intensive supportive care. A full treatment course consists of six cycles of R-CHOP at three weekly intervals.

Radiotherapy can also be used to treat DLBCL if there is a localised area of concern such as in spinal cord compression.

Lymphoma is very sensitive to treatment and one expects patients to show symptomatic improvement with the first treatment cycle. Treatment is given with curative intent, with an overall 5 year survival rate of 60% (10) therefore appropriate initial management and intensive care support if required, is fundamental to reducing morbidity and mortality from lymphoma.

Questions

1. Lymphoma can present with which of the following symptoms?

a) A lump in the neck
b) Breathlessness
c) A mass in the abdomen
d) Night-sweats
e) All of the above

2. What percentage of DLBCL cases involve an extra-nodal site?

a) 5%
b) 20%
c) 40%
d) 60%
e) 80%

3. Which of the following investigations is the most useful for diagnosing lymphoma?

a) LDH
b) FBC
c) CT chest, abdomen and pelvis
d) Tissue Biopsy
e) Urate

MANAGEMENT OF DIFFUSE LARGE B CELL LYMPHOMA IN THE ACUTE SETTING

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4. Which of the following is not a poor prognostic factor of DLBCL?

a) Age > 60 years
b) Elevated LDH
c) Performance status 3
d) 2 extra-nodal sites involved
e) Normal urate

5. Which medication would you prescribe to help prevent tumour lysis syndrome in a patient with lymphoma and urate within the normal range?

a) Rasburicase
b) Prednisolone
c) Rituximab
d) Allopurinol
e) Dexamethasone

Answers

1. All of the above
While lymphoma commonly presents as a nodal mass, patients often present late with advanced disease involving extra-nodal sites causing symptoms in multiple systems.

2. 40%
Extra-nodal dissemination is seen in up to 4 out of 10 cases of DLBCL.

3. Tissue Biopsy
While CT is mandatory to stage lymphoma, tissue biopsy is diagnostic and ultimately treatment will depend on the histological characteristic of the lymphoma,

4. Normal urate
Urate assists in stratifying risk of developing tumour lysis and is not a factor in the International Prognostic Index.

5. Allopurinol
Patients with urate less than 500umol should be started on Allopurinol 300mg daily, while those with higher levels should be given Rasburicase

Authors

Dr Ann O'Callaghan
Consultant Medical Oncologist
Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, PO6 3LY
ann.ocallaghan@porthosp.nhs.uk

Dr Alec Paschalis
Specialist Registrar in Medical Oncology
Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, PO6 3LY

Corresponding Author

Dr Alec Paschalis
alec.paschalis@porthosp.nhs.uk

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APPROACH TO MEDIASTINAL MASSES, DIFFERENTIAL DIAGNOSIS & MANAGEMENT

L Fox, A O'Callaghan

Abstract

Mediastinal masses represent a variety of conditions, benign and malignant. It is important to recognise clinical symptoms and signs that might point to a mediastinal mass, then investigate appropriately. We look at the case history of a lady found to have a mediastinal mass and review differential diagnoses and management.

Case Report

Mrs. N, aged 59, was referred to respiratory clinic for investigation following an abnormal chest X-ray (CXR) (figure 1) requested by GP to investigate recurrent chest infections and increasing breathlessness. She also had a persistent cough, producing thick yellow sputum with occasional blood and constant left sided chest pain. Her past medical history included diabetes, hypertension and a total abdominal hysterectomy for fibroids. Smoking history was approximately 30 pack years.

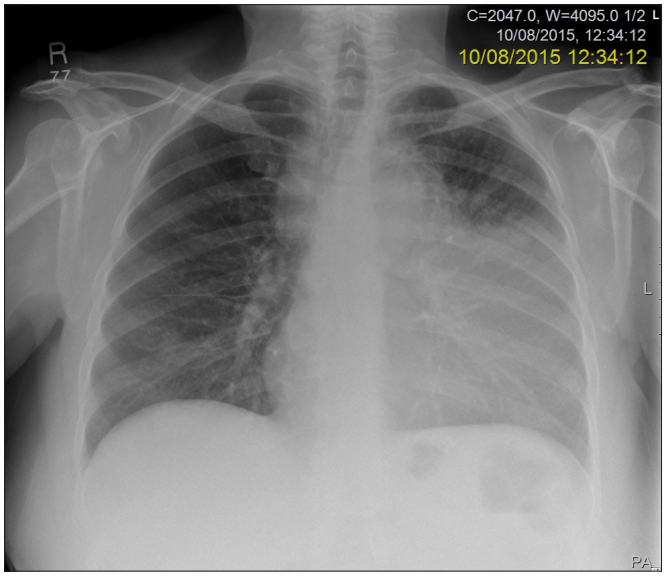

Figure 1: CXR at presentation.

Approach To Mediastinal Masses, Differential Diagnosis & Management
Patient Management

On examation she had no signs of Superior Vena Cava obstruction (SVCO). Chest was dull to percussion with no audible air entry on left side. There was a loud expiratory wheeze. Liver was palpable below right costal margin. Her performance status was ECOG 2 (capable of all self- care and up and about for at least 50% of day).

Full blood count was normal, as was sodium and calcium. Alkaline phosphatase and Lactate dehydrogenase (LDH) were elevated.

Respiratory work up included spirometry showing obstructive picture with FEV1 0.81 (42%), FVC 1.47 (64%). CT scan showed a large mediastinal mass invading the left upper lobe and carina with narrowing of the left main bronchus, lymphangitis, small left pleural effusion and hepatic metastasis.

Bronchoscopy revealed tumour in left main bronchus which was biopsied, demonstrating small cell lung cancer (SCLC). Radiologically she had extensive stage disease.

She was referred urgently to oncology for consideration of chemotherapy. She and her family were supported by lung cancer clinical nurse specialist (CNS) who she had already met at initial appointment. CNS provides and signposts information resources and offers ongoing supportive contact through disease course. SCLC generally will respond briskly to chemotherapy with rapid tumour reduction, however recurrence even after good initial response is inevitable and median survival is 6 – 12 months in treated extensive stage disease.

Mrs. N started palliative chemotherapy (Carboplatin and Etoposide) with the aim to shrink the cancer, provide symptom relief and increase her survival. Her symptoms improved within days of first treatment. She experienced significant side effects including vomiting, fluid retention and electrolyte abnormalities requiring admission for fluids and electrolyte correction.

CXR showed good disease response (figure 2) confirmed on CT after 3 treatment cycles. As Mrs. N improved both clinically and radiologically she will complete 6 cycles, with careful electrolyte monitoring and replacement as required.

APPROACH TO MEDIASTINAL MASSES, DIFFERENTIAL DIAGNOSIS & MANAGEMENT

L Fox, A O'Callaghan

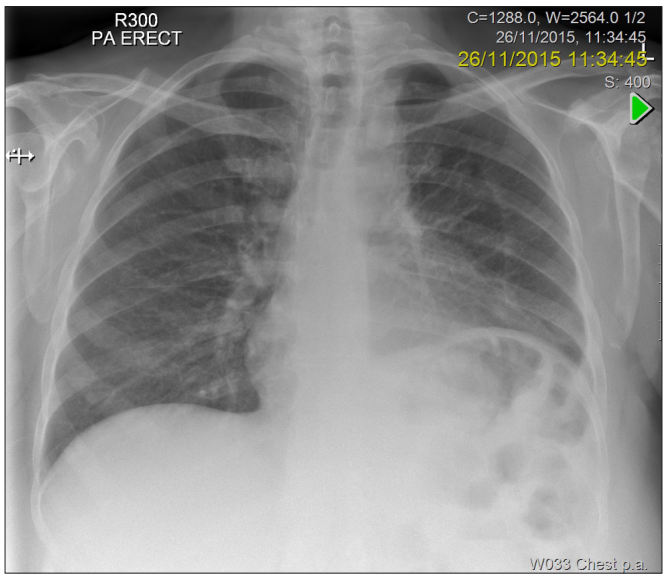

Figure 2: CXR post treatment – note PICC line in situ.

Discussion

The mediastinal borders are the sternum anteriorly, spine posteriorly, diaphragm inferiorly, thoracic inlet superiorly and lungs laterally (1). A mediastinal mass can be classified as anterior, middle or posterior depending on the location within the mediastinum. Classification is based on theoretical lines and compartments which are not physically separated by tissue planes, therefore masses aren't confined to one compartment (2). (See table 1.)

Causes of Mediastinal masses	
Anterior	Thymoma or thymic cyst Thyroid Lymphoma Germ cell tumour
Middle	Lymphadenopathy caused by: - Lymphoma - Lung cancer - Sarcoid Aortic arch abnormality Cysts
Posterior	Neurogenic tumour

Table 1

Patients can present with symptoms caused directly by the mass or systemic symptoms due to the underlying disease. Asymptomatic mass may be identified on a CXR or CT scan performed for an unrelated problem.

Symptoms caused by compression or invasion of mediastinal structures, as in this case, include cough, hemoptysis, and shortness of breath, chest pain, and stridor. Hoarseness occurs with recurrent laryngeal nerve compression and Horner's syndrome with sympathetic trunk involvement. Oesophageal compression can cause dysphagia. Acute presentation with SVCO or hypotension secondary to cardiac tamponade (1) is possible.

Systemic symptoms such as lymphoma 'B' symptoms, fever, night sweats or weight loss may give diagnostic clues. Symptomatic hyponatremia or hypercalcemia may be seen associated with lung cancer .Myasthenia gravis has a strong association with thymoma.

First concern with a mediastinal mass is of underlying malignancy. Time scale of symptoms may indicate aggressiveness of underlying process. Smoking history as in this case is pertinent. Mrs. N's smoking history immediately raised suspicion of lung cancer.

History of previous malignancy is important as malignant disease from other sites may metastasise to mediastinal nodes causing a mediastinal mass and in patients with a previous cancer history such as breast cancer, colorectal, prostate, melanoma it is highly likely that development of a mediastinal mass represents metastases from previous cancer but this should be confirmed histologically.

Initial ABC assessment is of Airway patency; check for stridor, Breathing; degree of respiratory compromise, Circulation looking for signs of impaired cardiac output or SVCO. Physical examination should note lymphadenopathy, organomegaly and testicular examination.

Abnormal CXR is investigated further with CT scan to define mass, its possible origin and degree of compression of mediastinal structures. Abdominal scan will detect liver metastases and infradiaphragmatic lymphadenopathy.

A CT scan will answer key questions:

1. Is mass is suitable for surgical resection or is there invasion of surrounding structures?

2. How best can a diagnostic biopsy be obtained? Options include bronchoscopy, percutaneous biopsy or surgically invasive approaches such as mediastinoscopy or video-assisted thoracoscopic surgery (VATS)

3. Is there an alternative site to biopsy e.g. liver metastases, peripheral pathological nodes?

APPROACH TO MEDIASTINAL MASSES, DIFFERENTIAL DIAGNOSIS & MANAGEMENT

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Mrs. N had a bronchoscopy as left main bronchus involvement was clearly seen on scan. An ultrasound guided liver biopsy of metastases was also an option.

Tumour markers, alpha-fetoprotein and beta-HCG should be checked if there is suspicion of germ cell tumour (1) .Hodgkin's lymphoma may be associated with high ESR. LDH may be elevated and this is a prognostic marker in Lymphoma, SCLC and germ cell tumours. Lung cancer may cause hyponatremia and hypercalcaemia.

Treatment of malignant mediastinal masses is specific to type of malignancy. Options to consider are chemotherapy, radiotherapy or symptomatic care only. Surgery is very rarely an option. Fitness for treatment, possible outcomes and patients views are important factors in decision making.

Radiotherapy is used for local control of tumour and can provide symptomatic relief of hemoptysis and airway obstruction. It is used when a rapid response to chemotherapy is not expected or if patient is unfit for consideration of chemotherapy. In this case because SCLC is very chemosensitive, chemotherapy was first choice treatment.

Lung cancer histologically may be SCLC or non-small cell lung cancer (squamous or adenocarcinoma) each being treated with specific chemotherapy regimen. Tumours with certain EGFR mutations may respond to targeted therapy with oral agents.

Lymphoma accounts for 20% of adult mediastinal masses (4). (fig 3 & 4) Lymphoma, Hodgkin's and Non-Hodgkin's are treated with curative intent according to histological type. Mediastinal malignant germ cell tumours are also curable with chemotherapy.

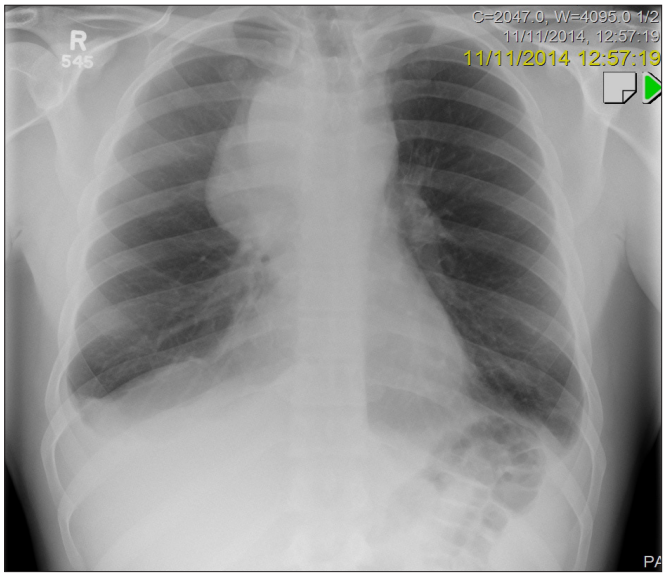

Figure 3: CXR Hodgkin's Lymphoma.

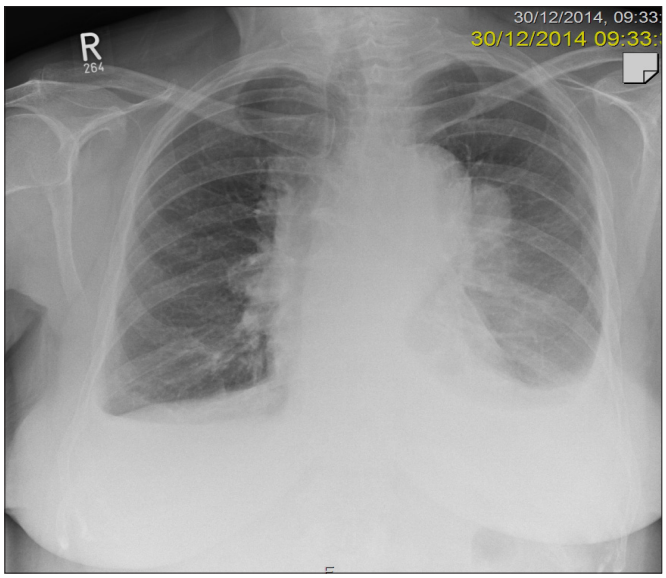

Figure 4: CXR: Non Hodgkin's Lymphoma

Thymoma, neurogenic tumours and malignant thyroid masses require specialist cardiothoracic and oncological MDT discussion to define role for surgery, radiotherapy and chemotherapy or radioiodine treatment in case of follicular thyroid cancer.

In summary, mediastinal masses have a wide range of differential diagnoses. Symptoms, history and blood work may give diagnostic clues. Management and outcome is wholly dependent on histological findings.

MCQs

1. Which of the following is not commonly associated with a mediastinal mass?

A. Asymptomatic
B. Horner's syndrome
C. Dysphagia
D. Night sweats
E. Vomiting

2. Which of the following is a possible cause of a middle mediastinal mass?

A. Thyroid mass
B. Lymphadenopathy
C. Neurogenic tumour
D. Thymoma
E. Germ cell tumour

APPROACH TO MEDIASTINAL MASSES, DIFFERENTIAL DIAGNOSIS & MANAGEMENT

L Fox, A O'Callaghan

3. What diagnosis is most likely in a 19 year old female with a mediastinal mass?

A. Germ cell tumour
B. Thyroid mass
C. Lung cancer
D. Hodgkin's lymphoma
E. Non-Hodgkin's lymphoma

4. What condition are thymomas most commonly associated with?

A. SIADH
B. Addison's
C. Myasthenia Gravis
D. Cushing's Disease
E. Diabetes

5. What percentage of anterior mediastinal masses are germ cell tumours?

A. 1%
B. 5%
C. 10%
D. 15%
E. 20%

Answers

1. Answer: E
Asymptomatic masses are not uncommon. Dysphagia and Horner's syndrome are compressive symptoms. Lymphoma commonly causes night sweats.

2. Answer: B
The middle mediastinum contains the heart, great vessels including aorta and vena cava, trachea and main bronchi and lymph nodes. The most common cause of a middle mediastinal mass is lymphadenopathy (1)

3. Answer: D
Hodgkin's lymphoma is the commonest malignancy in teenagers and young adults. It commonly presents with a mediastinal mass which may be associated with cervical, supraclavicular or axillary lymphadenopathy which if present represent accessible biopsy sites. Mediastinal disease is most usually of nodular sclerosing histological subtype

4. Answer: C
20-25% of patients with a thymoma will, at some stage, develop Myasthenia Gravis (MG), while 10-20% of patients with MG will have a thymoma7. All patients with thymomas should be investigated for MG as it can affect how patients respond to medication e.g. anesthesia. Surgery is required to remove the thymoma and patients will require ongoing treatment for MG.

5. Answer: D
The commonest mediastinal germ cell tumour is benign teratoma which is usually surgically resected (5). Malignant germ cell tumours show male predominance, and investigations for primary gonadal malignancy are essential.

Authors

Dr Lauren Fox
CT2 Medicine, Queen Alexandra Hospital, Portsmouth, PO6 3LY
Lauren.Fox@porthosp.nhs.uk

Dr Ann O'Callaghan
Consultant in Medical Oncology, Portsmouth Oncology Centre
Queen Alexandra Hospital, Portsmouth, PO6 3LY

Corresponding Author

Dr Ann O'Callaghan
Ann.o'callaghan@porthosp.nhs.uk

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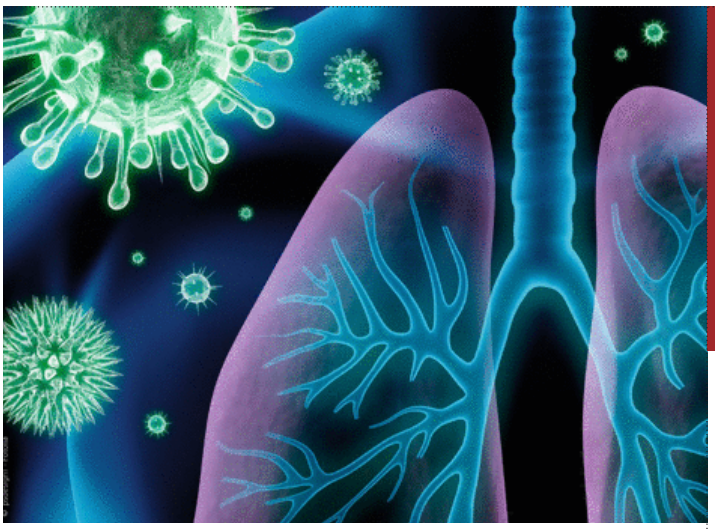
CANCER OF UNKNOWN PRIMARY

J Patel, E Marshall



Abstract

Cancer of unknown primary (CUP) represents a spectrum of metastatic cancers that present without a clear primary site (1) and is one of the top ten most common cancers in the U.K. (2) It is an aggressive disease, which by definition, presents with advanced stage and is associated with a poor prognosis (1,3). Patients with CUP may present via a number of different referral routes (4) and a diagnosis is often accompanied by considerable anxiety and distress for the individual. (2) Investigation, diagnosis and management can often prove complex and lengthy. (2,4) This paper will explore the clinical presentation, initial investigations and management of the disease including recommendations from the National Institute of Clinical Excellence (NICE) to improve patients' care and clinical outcomes.

Introduction

Cancer of unknown primary (CUP) is a term used to encompass a group of heterogenous metastatic cancers in which a primary site has not been identified after a standard set of investigations. (1,3,4)

CUP is a relatively common presentation and represents around 5% of all invasive cancers. (5) Over 10,000 people died from CUP in 2012 (6), making it the 4th most common cause of cancer deaths in England and Wales. (4) It is considered an aggressive form of cancer and has been found to have a poorer prognosis than those with metastatic cancer of known primary. (7,8)

There may be a number of reasons for a lack of detectable primary, including: the tumour being so small it is clinically undetectable, the primary tumour disappearing after seeding or the tumour being destroyed by the body's immune defences. (2,9). Irrespective of the causality, CUP represents malignancy with a high metastatic potential that results in cancer presentation with late stage disease and the primary producing no localising symptoms. (3)

Cancer Of Unknown Primary
Patient Management

NICE defines CUP as a clinical spectrum that is dependent on the extent of clinical evaluation and diagnostics. Patients with suspected metastatic cancer detected on limited examination are defined as having malignancy of unknown origin (MUO). (4) A poor performance status patient with widespread liver metastases detected on liver ultrasound may not be appropriate to consider further extensive investigation. Patients with histological evidence of malignancy are defined as provisional CUP (pCUP) prior to completion of all necessary investigations to rule out a primary (confirmed CUP). (4)

The definitions do not simply reflect semantics but are highly relevant in the context of clinical management and accurate incidence reporting. A diagnosis of CUP requires histological evaluation and in many cases, formal biopsy may not be indicated if this does not impact on management decisions for the patient. (4)

CUP can be classified pathologically into:

1. Epithelial Cancers

a) Adenocarcinomas

b) Squamous cell carcinomas

2. Poorly or undifferentiated neoplasm;

3. Carcinoma of neuroendocrine origin (1,3)

Due to the varied metastatic sites of involvement, patients with CUP may present via multiple routes and often with general non-specific symptoms, (3) therefore leading to diagnostic difficulties.

The non-specific nature of its presentation often leads to a lengthy investigative process and inappropriate referrals to a range of site specific services with inevitable delay in diagnosis and subsequent treatment. (4)

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Clinical presentation

The disseminated pattern of the disease at presentation often means the absence of any localising clinical signs relating to a primary tumour site. (10)

Some documented symptoms and signs of those with CUP include: unexplained weight loss, general deterioration, loss of appetite, fatigue, lump or bone pain. (10,11) Multiple areas of involvement are seen in over half of patients, with common areas of metastases being bone, liver, lungs and lymph nodes, metastases however, can occur at any site. (3) Anecdotally, in clinical practice the most common pattern of presentation is liver metastases (abdominal pain and deranged liver function tests), brain metastases (stroke-like syndrome) or bone metastases (bone pain or fracture).

Initial investigations

The extent of investigation in CUP is highly dependent on the therapeutic options available and every effort should be made to determine the patient's wishes and fitness for treatment (4). In some instances, the diagnosis may be clinched by a thorough history and examination (3,12) which may detect a neglected primary breast cancer, for example. This should include a breast, genital, rectal, pelvic, skin and nodal area examination with the aim of attempting to locate a primary site without the need for extensive investigations. (3,4,12) Due to the broad variations in clinical symptoms of the patient, a standardised set of investigations is inappropriate. NICE have developed recommendations for initial diagnostic investigations that highlight specific patterns of CUP presentation. It should be used where clinically appropriate and directed by the individual's presentation (4). These are shown in box 1.

1. History and examination (should include: breast, nodal areas, skin, genital, rectal and pelvic examination)
2. Bloods: full blood count, urea & electrolytes, liver function tests, calcium & lactate dehydrogenase.
3. Myeloma screen
4. Urinalysis
5. Chest X-ray
6. Computed tomography (CT) chest, abdomen and pelvis
7. Prostate Specific Antigen (PSA) in men, CA 125 in women, human chorionic gonadotrophin (hCG) & alpha-fetoprotein (AFP) where appropriate
8. Testicular ultrasound in men presenting with possible germ-cell tumours
9. Biopsy and histological examination where necessary

Box 1: Initial diagnostic phase investigations for CUP recommended by NICE (7)

Secondary investigations should be based on clinical presentation and pathological findings in appropriate patients. (3,4)

Prognosis and Service recommendations

Patients with CUP do not easily fit into a site-specific referral pathway. There is a general lack of designated services and often a lack of clinical ownership. This can lead to an absence of support, increased hospital stays and a delay in management. Against this background, patients often find themselves passed from one multidisciplinary team (MDT) to another, resulting in poorly coordinated care, delayed management and heightened distress. (2,4)

In 2010, in recognition of the unsatisfactory care pathway, NICE issued guidance that outlines recommendations in order to improve patient care and outcomes. The recommendations are underpinned by early specialist advice and management decisions according to patient fitness, patient's wishes and therapeutic options. (4) A summary of the main recommendations are shown below in box 2. These are aimed in providing dedicated services to those with CUP, bringing the care and management in line with other cancers. (4)

• Every hospital should have access to a CUP team.
• Every hospital should have access to a CUP specialist nurse or key worker.
• Patients should be referred as an outpatient on a '2 week referral' basis for assessment by the CUP team if they are suspected of having CUP.
• Only perform investigations if: the results are likely to affect a treatment decision, the patient understands why they are being undertaken and they understand the benefits/risks of the tests and treatment.
• A multidisciplinary team should be set up to review the treatment of care of those diagnosed with CUP.

Box 2: Summary of NICE guidance recommendations 2010 (4)

Treatment

Treatment of those diagnosed with CUP should be provided on an individual basis and tailored according to the clinical-pathological subtype. (1) Therapy may include chemotherapy (the mainstay of treatment in those with metastatic disease), surgery or radiotherapy and is guided by the pattern of presentation, performance status, histology and estimated prognois (4,9,10).

Early access to symptom control and palliative care services form an integral part of the management of those with CUP and when delivered as part of a coordinated CUP service, may result in significant shortening of hospital stay. (4,13).

CANCER OF UNKNOWN PRIMARY

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Conclusion

Cancer of unknown primary is a common disease associated with a poor prognosis (2,3) and can prove a diagnostic and treatment challenge. (10) CUP often presents via a number of routes and with general non-specific symptoms leading to diagnostic and treatment delays. (3,4)

Patients with suspected CUP should undergo a limited number of baseline tests according to the clinical presentation and should also be referred at an early stage to the CUP services for further assessment and management. (4)

Best of 5 Multiple Choice Questions

1. A patient attended his GP with right upper quadrant abdominal pain. He is found to have abnormal liver function tests and a CT scan is suspicious of liver metastases. What would be the appropriate next step in management?

A. MRI liver

B. Refer for endoscopy

C. Liver Biopsy

D. Follow up CT in 2 months

E. Refer to CUP team

2. A 56 year old female presents to their GP with fatigue, weight loss and a lump in her groin. Her GP organizes a CT chest, abdomen, pelvis and an ultrasound biopsy of the lump in her groin. From these tests she is found to have disseminated metastatic disease to the lungs, liver and bone. The biopsy results show an adenocarcinoma of unknown origin. Her GP decides to refer her to the local CUP service for further evaluation. What is this patient's current clinical diagnosis?

A. Metastatic lung cancer

B. Malignancy of unknown origin

C. No diagnosis can be made

D. Provisional Cancer of Unknown Primary

E. Confirmed Cancer of Unknown Primary

3. An 88 year old patient presents with rapid weight loss, anaemia and feeling generally unwell. A CT shows liver, lung and bone metastases. The patient is very frail and has performance status 3. What would be the preferred next step?

A. Explain the likely diagnosis to the patient and focus on symptom management

B. Tissue biopsy

C. Referral for urgent chemotherapy

D. Referral to the specialist lung team

E. Request for a PET CT scan

Answers

1. E, Refer to CUP team

This patient has a clinical picture that is consistent with a diagnosis of malignancy of unknown origin (MUO). In order to facilitate assessment, further investigation and treatment it is recommended that these patients should be referred immediately to the CUP team for assessment within two weeks. The CUP team can then evaluate whether further tests such as an MRI liver or biopsy would be appropriate. (4)

CANCER OF UNKNOWN PRIMARY

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2. D, Provisional Cancer of Unknown Primary

According to NICE guidance, as the patient has had an initial series of investigations, a confirmed malignancy on histological evaluation but has not currently been reviewed by a specialist or had more specialised tests, the patient has a provisional CUP diagnosis. This will be changed to a confirmed CUP diagnosis once the patient has been seen by the CUP team and any further appropriate investigations have been completed.(4)

3. A, Explain the likely diagnosis to the patient and focus on symptom management

This patient has widespread advanced metastatic cancer. Performance status scales such as the Eastern Cooperative Oncology Group (ECOG) scales can be used aid prognosis evaluation. (14) The clinical picture of this patient together with her performance status indicates that she has a poor prognosis.

Management aims would therefore be symptom control; with a focus on maintaining quality of life. (1) It is also important to inform patients and their families of the diagnosis and management goals to reduce distress and anxiety. (4)

Authors

Jenika Patel
Foundation Year 2 Doctor
Royal Liverpool Hospital,
Prescot Street,
Liverpool, L7 8XP
jenikapatel@doctors.org.uk

Ernie Marshall
Consultant in Medical Oncology
Clatterbridge Cancer Centre,
Clatterbridge Road, Wirral,
Merseyside, CH63 4JY

Corresponding Author

Ernie Marshall
Ernie.marshall2@clatterbridgecc.nhs.uk

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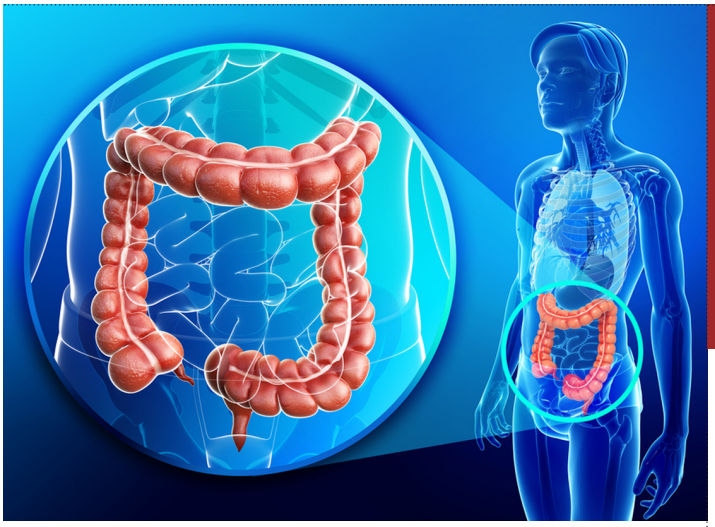
CASE BASED DISCUSSION: MANAGEMENT OF COLORECTAL CANCER

H Joyce, K Chan, A Dewdney



Abstract

A 44-year-old man with known history of metastatic colorectal cancer developed signs and symptoms of obstruction during treatment with palliative chemotherapy. He had originally presented 7 months prior to this with acute bowel obstruction as a consequence of his colorectal cancer and was fitted with a colonic stent.

This case discusses subsequent management of his malignancy, the specialists involved and the treatment options available for colorectal cancer.

Case History

A 44-year-old man was admitted to hospital with abdominal pain. He had developed worsening constipation over the past 6 weeks and had not opened his bowels for 2 days. In the preceding 24 hours he developed severe, spasmodic abdominal pain, bloating and vomiting.

Seven months earlier he had been diagnosed with bowel cancer with metastases in the liver. He had presented as an emergency with bowel obstruction secondary to a tumour in his colon on a background of 8 months of altered bowel habit. His presenting bowel obstruction was managed with the insertion of a colonic stent, which relieved his symptoms.

His initial staging investigations revealed widespread liver metastases throughout both lobes of his liver, this meant that he was not suitable for radical resection of his primary and liver metastases. He had therefore been treated with palliative Folinic acid, 5-FU and Oxaliplatin (FOLFOX) chemotherapy for 7 cycles until unfortunately he had developed worsening abdominal symptoms as described above.

Case Based Discussion: Management of Colorectal Cancer
Patient Management

Prior to his diagnosis of metastatic bowel cancer his only past medical history of note was well-controlled asthma. He took salbutamol and had no known drug allergies. He had no family history of bowel pathology or other cancers. He had previously worked full time as a cleaner, drank minimal alcohol and was a non-smoker.

On examination he was pale with a low BMI. He had abdominal distention, generalised tenderness with no guarding and no audible bowel sounds. Given his history he was treated as a bowel obstruction and an abdominal x-ray was arranged (Figure 1). This showed distended gaseous loops of large bowel with heavy faecal loading within the caecum. The previously inserted colonic stent was seen with no evidence of gas within the bowel below the stent.

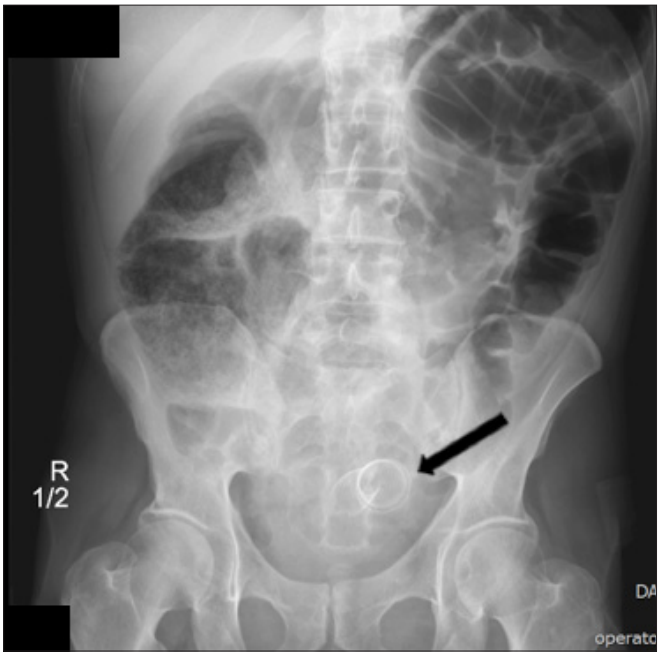


Figure 1: Abdominal X-ray: Dilated loops of bowel proximal to a colonic stent.

CASE BASED DISCUSSION: MANAGEMENT OF COLORECTAL CANCER

H Joyce, K Chan, A Dewdney

He went on to have a computerised tomography (CT) staging scan of his thorax, abdomen and pelvis which showed improvement in the size of his liver metastases but worsening stenosis from tumour progression around the distal end of the colonic stent. He went on to have a further colonic stent inserted (Figure 2) to treat his recurrent obstruction and then proceeded to second line palliative chemotherapy.

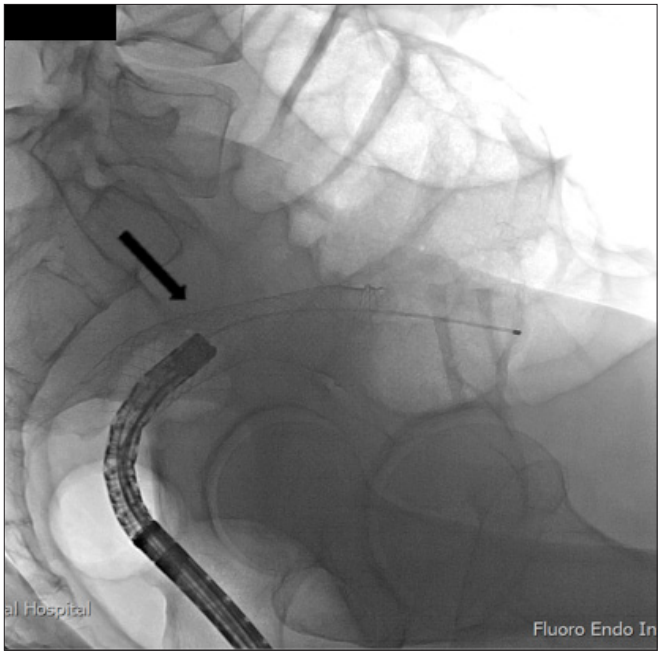


Figure 2: Fluoro-endoscopic image taken during second colonic stent insertion.

Discussion

Colorectal cancer (CRC) is the 4th most common cancer in the UK with an increased incidence of 6% over the last decade. In 2011 alone there were 41,581 new cases (1).

Ninety five percent of patients diagnosed are over the age of 50 and on average there is a 5 year survival of 50.7% (2)

There is a clear correlation of increased survival and cure with earlier detection as seen in the table below. In light of this a screening programme was developed and is now standard thoughout the UK since April 2006. People from the age of 60 -74 are sent out faecal occult blood tests via the post on a 2 yearly basis (3). A positive test results in a 2-week urgent referral for colonoscopy.

Staging	5 year survival
Dukes A	85-95%
Dukes B	60-80%
Dukes C	30-60%
Dukes D	<10%

Table 1: 5 year survival statistics for colorectal cancer.

Common symptoms of bowel cancer include, blood on wiping after defecation, blood mixed in with stool, change in bowel habit, faeculent vomiting or in extreme circumstances with obstruction and even bowel perforation. Patients can also present with iron deficiency anaemia or symptoms of more widespread disease such as weight loss, shortness of breath or jaundice.

Risk factors include increased red meat diet, obesity, smoking and alcohol intake. There is also an increased incidence in those with inflammatory bowel disease and type 2 diabetes mellitus (4,5). Approximately 5% of bowel cancers have a known genetic component due to familial adenomatous polyposis or hereditary non polyposis colorectal cancer.

Most colorectal cancers are diagnosed by flexible sigmoidoscopy/ colonoscopy which allow direct visualisation of the bowel lumen in addition to biopsy. CT scanning of the chest, abdomen and pelvis is used to stage colon cancers; however MRI imaging of the pelvis is required for rectal cancers as it allows more accurate staging and informs decision-making about the need for neoadjuvant radiotherapy.

The main stay of treatment and cure of early bowel cancer is surgical resection. Depending on the type of operation required there may be potential long-term implications such as managing a colostomy as well as changes in bowel habit. All of which can cause significant lifestyle changes and psychological distress.

In patients with liver-only metastases surgical resection of the liver lesions is now considered and in some cases can lead to cure. Depending on the location and the extent of the disease in the liver a hepatobiliary surgeon may perform liver surgery. These are complex treatment decisions and need to be discussed at an experienced multi-disciplinary team meeting (MDT).

CASE BASED DISCUSSION: MANAGEMENT OF COLORECTAL CANCER

H Joyce, K Chan, A Dewdney

The use of chemotherapy is divided into three settings:

1.) In the neo adjuvant setting (i.e. pre operatively) chemotherapy is used concurrently with radiotherapy for rectal cancers or as downstaging in resectable CRC with liver metastasis.

2.) In the adjuvant setting (i.e. post operatively) chemotherapy can be used to reduce the absolute risk of recurrence in the region of 5 - 15% depending on the regime of chemotherapy.

3.) In the palliative setting it is used largely to help with symptoms, improve quality of life and overall survival.

The main chemotherapy regimens used in colorectal cancer involve an antimetabolite (5 Fluorouracil or capecitabine) often in combination with either oxaliplatin or irinotecan. The common toxicities include diarrhoea, infection (including neutropenic sepsis), mucositis , palmar plantar erythema, sensory neuropathy (secondary to the oxaliplatin).

In the era of personalised medicine targeted treatments such as agents inhibiting vascular endothelial growth factors are used in combination with chemotherapy, namely Bevacizumab and Aflibercept. The main side effects of these drugs include hypertension, proteinuria and wound healing issues. Other targeted agents include cetuximab and Panitumumab which are epidermal growth factor receptor inhibitors used in patients who are RAS wild type. The most common side effect is diarrhoea and an acniform rash. These drugs are not currently available on the NHS for 1st line treatment of metastatic colorectal cancer.

Radiotherapy is used mainly in downstaging rectal cancers prior to an operation (i.e. neoadjuvant setting) or in palliative setting to specific local areas such as bone metastases.

Selective Internal radiation therapy (SIRT) is a relatively new treatment. It involves delivering millions of microscopic radioactive spheres, directly to site of liver tumours, where they selectively and directly irradiate the tumours. This is currently used in patients with liver-predominant metastases following progression on chemotherapy.

The median survival for an incurable colorectal cancer is around 6-9 months when left untreated. When treated with chemotherapy this can potentially increase to between 18-24 months.

During the initial consultation it is very important to try and elicit the expectations and wishes of a patient. In the palliative setting some people value their quality of life more than quantity and worry that chemotherapy may significantly deteriorate their general wellbeing for however much time they have left. Overall, each case has to be treated on an individual basis. All new cases of cancer need to be discussed in an MDT this discussion should include the tumour stage, patient fitness and co-morbidities. Final treatment decisions must take into account the patients' own ideas, concerns and expectations.

To end we will discuss the acute management of bowel obstruction. It is always prudent to do your systemic review of airway, breathing and circulation in assessing how unwell the patient is. You should place the patient 'nil by mouth' and consider insertion of a nasogastric tube to decompress and relieve the pressure caused by the obstruction.

Always consider the patient's comfort and ensure adequate analgesia is prescribed. This will not only help the patient symptomatically but will also aid in attaining more accurate diagnostic imaging. They will initially require an abdominal x-ray ultimately leading on to a CT scan. On confirmation of obstruction on imaging you would need to ensure that your relevant senior doctor is informed and progress to discussion with the general surgeons.

The options for further treatment may include conservative management with IV fluids and bowel rest, stent insertion or operative options potentially resulting in stoma formation. Depending on the chosen management for the patient's bowel obstruction consideration should then be given to any further support required which can range from stoma nurse review to dietetic management.

MCQ's

1.) Which of the below are symptoms of bowel obstruction?

a. Faeculent vomiting

b. Abdominal pain

c. Reduce/absent bowel sounds

d. Constipation

e. All of the above

CASE BASED DISCUSSION: MANAGEMENT OF COLORECTAL CANCER

H Joyce, K Chan, A Dewdney

2.) When a patient is diagnosed with bowel cancer and metastases to the liver their management is likely to:

a. Always be palliative due to the metastatic nature of their disease

b. Include external beam radiotherapy

c. Mean SIRT would always be a better treatment option for the liver metastases than surgery

d. Mean there is potential for curative options if the liver metastases are resectable

e. Always involve chemotherapy

3.) A 55 year old woman on the acute medical ward has just been diagnosed with metastatic colorectal cancer. Your medical student asks you what her likely median survival is without treatment:

a. Weeks – 3 months

b. 3-6 months

c. 6-9 months

d. 12-18 months

e. 18-24 months

4.) A 64-year old male patient attends your GP surgery. They have recently attended a funeral for their cousin who died of bowel cancer and want to know how they can reduce their chances of developing this. What would you advise them?

a. Reduce their dietary intake of red meat

b. Maintain a healthy BMI and take regular exercise

c. Stop smoking

d. Reduce their alcohol consumption

e. All of the above

5.) You see a patient whilst attending an oncology clinic. She has completed resection of her bowel cancer and is about to commence adjuvant chemotherapy including an antimetabolite drug 5-FU. Apart from changes in her red cell, white cells and platelets she asks what the most common side effects are:

a. Diarrhoea, nausea and vomiting, mucositis and palmar plantar erythema

b. Diarrhoea, liver dysfunction and alopecia

c. Diarrhoea, angina and rashes

d. Nausea and vomiting, liver dysfunction, fatigue

e. Nausea and vomiting, loss of fertility and headaches

Answers

1. ANSWER: 1e.

Bowel obstruction can present as a gradual process (subacute) with reduced bowel motion, nausea and abdominal distension. It is often misdiagnosed as constipation. It can present acutely like this gentleman with vomiting, and in severe cases faeculent vomiting. Reduced bowel sounds are a late sign. Abdominal xray is usually the first standard quick radiological investigation often followed by a CT.

2. ANSWER: 2d.

When a patient has liver metastases this means there may potentially be curative options for them. The most important factor is whether the disease is limited to the liver, if there is extra-hepatic disease then liver surgery is usually not offered. The final decision regarding suitability for liver resection remains the surgeon's and is usually based on being able to leave at least 30% functioning liver behind after resection. In addition to this the patients age, performance status and co-morbidities must be considered ie are they fit for surgery and a general anaesthetic? This will have to be discussed at an MDT.

SIRT is an option considered for inoperable liver metastases. In the best cases it can be used to reduce the size of a metastasis in the hope that it may become resectable. However, it is more often used in a palliative setting to improve symptoms and increase time to progression (6,7).

CASE BASED DISCUSSION: MANAGEMENT OF COLORECTAL CANCER

H Joyce, K Chan, A Dewdney

3. ANSWER: 3c.

4. ANSWER: 4e.

All of the listed answers put you at an increased risk of bowel cancer. You would encourage them to participate in the bowel cancer screening programme – people who take part in this have a 16% lower risk of dying from bowel cancer (4). In addition you should take a full family history and if they have a 1st degree relative under 45 years old or 2 first degree relatives of any age it may be worth discussing them with your local genetics service. People who are at higher risk of bowel cancer may be considered for regular colonoscopy.

5. ANSWER 5a.

All of the above are possible side effects related to treatment with 5-FU chemotherapy. However, the most common side effects (10% or greater) are diarrhoea, nausea and vomiting, mucositis, palmar plantar erythema and arrhythmias. Less common side effects (between 1 and 10%) include hair thinning, rashes, anorexia and loss of fertility. Rare side effects (<1%) include angina and MI, total alopecia, liver dysfunction and headaches (8).

Authors

Helen Joyce
Clinical Oncology Specialist registrar
Weston Park Hospital Whitham Road, Sheffield, S10 2SJ
helen.joyce@sth.nhs.uk

Kevin Chan
Medical Oncology Specialist registrar
Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ

Alice Dewdney
Consultant Clinical Oncologist
Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ
alice.dewdney@sth.nhs.uk

Corresponding Author

Kevin Chan
kevin.chan@sth.nhs.uk

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DEVELOPING A FOUNDATION TASTER

JL Kahan, M Button, R Adams, S Cox, A Voyle-Smith

Developing A Foundation Taster
Teaching & Training

The Foundation Programme encourages trainees to experience a 'Taster' to help plan important career decisions. But what is a Taster? Why would you want to do a Taster and how would you go about organising it? This article will give you all this information and a working example of a successful Taster programme that has been developed in Oncology at Velindre Cancer Centre in Cardiff.

What is a taster?!

A taster is defined by the Foundation Programme as a period of time, usually two to five days, spent in a specialty in which the Foundation trainee has not previously worked.

The concept was developed in the context of The Collins Report, 2010, which evaluated the Foundation Programme. The report recommended, that "tasters" should be promoted for foundation year (FY) trainees, if they had an interest in a clinical area but were unlikely to have the opportunity to rotate to that specialty. It defined a taster in terms of effective and efficient learning in an appropriately supported and supervised environment. This key recommendation has led to a small number of hospitals and departments developing a structured taster programme. Whilst taster programmes are not universally available, we would suggest that with a little bit of planning it is possible to develop your own taster which will help you make important career choices as well as improve your CV and secure your next job!

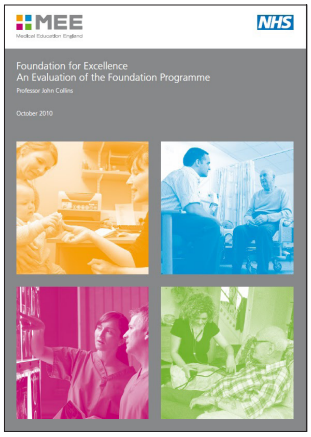

Figure 1: The Collins report 2010. "A taster enables an insight into the work of the specialty"

Why do a taster?

Some junior doctors will be fortunate to know the career path they wish to follow. A taster is objective evidence of a trainees' commitment to the specialty, and will ensure a good understanding of what the specialty entails. Many foundation trainees will have only a general idea of which specialty is of the most interest to them. Often career decisions have to be made prior to completing rotations and fairly early in training. For example, applications for Specialty Training (ST) open in November, only a third of the way through FY2. Similarly, for higher ST3 training, applications open in February. A taster placement can give excellent exposure to a specialty of interest which can help focus key career decisions.

NHS Medical Careers advise that when planning your career, use a framework to enable well informed career decisions . Experience of a taster shows that you have considered your career and had the motivation and organisational skills to arrange specific work experience.

Tasters can also be used to develop and focus a CV which can improve the likelihood of successful applications in higher training. Most Foundation Year (FY) doctors will have very similar achievements and it can be difficult to stand out. Attendance at a taster shows motivation and dedication towards a specialty. These are key attributes which are assessed on the application form and in interview and form a key part of 'Person Specifications' in many specialties - see Table 1.

If a trainee is involved in the initial planning/initiation of a taster programme this will be an excellent example of developing a service and implementing change. These are skills often looked for in application forms and at interview.

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Commitment to Specialty – Learning and Personal Development		
Essential criteria	**Desirable criteria**	**When evaluated**
-Shows initiative/drive/enthusiasm (self-starter, motivated, shows curiosity, initiative)	Extracurricular activities / achievements relevant to the specialty	Application form Interview/selection centre References
- Demonstrable interest in, and understanding of, the specialty - Commitment to personal and professional development	Evidence of participation at meetings and activities relevant to the specialty Evidence of attendance at organised teaching and training programme(s)	
- Evidence of self-reflective practice		

Table 1: 2010 Person specification: common to applicants in Core Medical , Core Surgical and ACCS . These criteria are also specified for higher specialty training in Clinical and Medical Oncology.

How to organise a taster

A taster may be advertised via your deanery by emails or on their website. Velindre Cancer Centre runs an oncology taster week three times a year. Invites for applications are sent by email via the deanery. The medical education department also advertises on their website. If you have a specific clinical interest, familiarise yourself with the relevant department as well as your postgraduate medical education centre and with any associated websites. Contact your deanery -try the postgraduate training manager - who may have information on taster programmes that are currently running.

The Foundation School Directors will have a register of local tasters that are already in place . If a taster already runs in the area of interest sign up early and get study leave arranged. If you would like to develop a taster programme discuss the idea with clinical and educational supervisors. They may have some useful advice! There may be a consultant who acts as the faculty career lead in the trust, who will work with the postgraduate medical education department. If a taster is not currently running they may be eager to develop a programme as it aids their fulfillment of key recommendations. The Local Education and Training Board (LETB) may also be able to offer advice.

An alternative option would be to contact the relevant department or a particular consultant. Some Consultants will have a greater interest in teaching, ask around and ask colleagues. Most consultants will be pleased to have someone who is enthusiastic and interested. If they require further information on developing a taster, the Foundation Programme website and the Reference guide 2012 specifies the supervisor's role in the development of a taster. See Box 1.

The UK Foundation Programme Office.

The foundation Programme Reference Guide 2012. A summary of what a taster involves for Clinical and Educational Supervisors.

The Foundation Programme. The website has a careers section where a list of career advisors for each Deanary and Local Education and Training Board (LETB can be found).

Box 1: Useful web sources advice to help set up a taster.

Planning ahead to structure the taster will improve its value. For example an Oncology taster should include exposure to outpatients and inpatients, radiotherapy as well as chemotherapy and palliative care. Bearing specific learning objectives in mind will produce a more structured programme, aligned to the aim of supporting an informed, long term career choice.

A consultant should have overall supervision but the experience should not be limited to an individual's timetable. If a taster is already in place but does not include a specific area of interest enquire to see if it can be incorporated. As a junior doctor you will have access to study leave days and a limited budget. A taster will not reduce the budget and can be covered by study leave. However, apply for study leave early to ensure that there are not gaps on the rota and avoid last minute cancellations, or annoying your colleagues.

How should it be structured?

Firstly, this depends on what experience you wish to gain. Clearly, a taster in nephrology will differ to that of psychiatry but the aim will be to provide an overview of what higher training (and ultimately being a consultant) will involve.

Outpatients

Almost all specialties will have outpatient clinics. We suggest a taster should incorporate at least two clinics. Clinic time is often limited as a foundation trainee, and even as core trainee. Use this as an opportunity to see how the vast majority of patients are managed. Try to get involved, ask questions, clerk new patients and discuss with a supervising consultant.

Inpatients

Attend the team ward round, but don't let yourself just get roped into ward jobs, the aim is to be getting experience outside your usual responsibilities.

DEVELOPING A FOUNDATION TASTER

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The Multi-disciplinary team

Consider a session with non-doctor colleagues: E.g pharmacists, echo-sonographers, physiotherapists, Specialist Nurses, radiotherapists etc. Again this is dependant on the specialty applied for. This will give you a broader understanding of the roles within a specialty and an opportunity to meet with experts in their own field.

Specialty-specific experience

An example in an oncology taster would be to attend and have a go at radiotherapy planning (you won't be responsible for the final product, so don't worry) as well as the radiotherapy review clinic, chemotherapy ward and visit to the pharmacy aseptic department.

Velindre Cancer Centre in Cardiff has a well run taster programme operating since 2011. An example of the timetabled week is found in table 2. Feedback showed that 100% of attendees rated the Taster week as a 'very useful' insight into the specialty.

	AM	PM
Monday	9:00am Sign in & Badge Main Switchboard 9.30 Main Outpatients Clinic	1.30 Main Outpatients Clinic
Tuesday	9.00am Tour of Velindre Cancer Centre 10.30 – 12.00noon Radiology Introduction & Tour	1.00 – 2.00 Nuclear Medicine 2.00pm Head & Neck Clinic
Wednesday	8.30 MDT 10am Breast Chemo Clinic Main Outpatients 11:30 – 12:30 Radiotherapy Tour & Introduction	2.00pm Pharmacy Talk 3:00 – 4:00 Careers Talk
Thursday	9.00am Gynae Brachytherapy 1.00pm Physics Treatment Planning	2pm Clinical Trials Introduction & Tour
Friday	9.00am Lung Radiotherapy Planning Meeting 10am Chemo Clinic Main Outpatients	12.30 Acute Oncology Service (AOS) Meeting & Shadow on Call SpR for the afternoon

Table 2: An example of an oncology taster from Velindre Cancer Centre.

Each session has a named lead and contact details are provided. The timetable includes clinics, multi-disciplinary team meetings and talks from specialty registrars and training leads. Visiting departments such as pharmacy and radiotherapy gives a real sense of what specialty training involves.

Benefits for the Department

The promotion of tasters at both F1 and F2 level was one of the key recommendations of the evaluation of foundation training. This implies that the deanery and LETB should be supportive of a taster, as it will help them achieve key recommendations!

A further benefit for the LETB includes possibly improved recruitment into specialty training. In South Wales prior to the introduction of the taster programme only 67% of speciality training posts were filled, from 2014 all posts were filled. A taster was one of a number of innovations used locally to try and improve the recruitment process.

Once a taster has been established subsequent placements can follow the same format and will be simpler to role out as the department can use the first timetable as a template for the next trainees, making each successive taster easier to organise. It will also be registered by the Foundation School as a taster available for FY trainees.

Key points:

- *A taster is an excellent way to gain experience in a particular area*
- *Your place of work should support your study leave*
- *Plan ahead and apply for study leave early*
- *Recruit a enthusiastic consultant and contact postgraduate medical education*
- *Develop a timetable with a point of contact for each session*
- *Use the experience to reflect and develop your career*
- *Add to CV and application forms to show commitment to specialty*

Further considerations

If after a taster the outcome is that the chosen specialty is not for you, this should not be seen as a negative outcome. It would be much worse to embark on a training programme only to find out it's not right further down the line.

Ensure the experience is beneficial by reflecting on how it has changed career plans. Use it to promote yourself in application forms, CVs and at interview.

DEVELOPING A FOUNDATION TASTER

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Best of five questions

1. Which of the following statements is not correct with regard to taking part in a taster week?

A - Discussion with your consultants and the medical education department is important.

B - The Foundation Schools hold a register of tasters which can be accessed by trainees.

C - A taster can be used to gain further experience in a clinical area of interest and used to guide career choices.

D - The deanery should support the application to do a taster.

E - If a taster is not currently running it is not possible to set up your own.

2. Which one of the following statements regarding participation in a taster week is true?

A - It is of no benefit in career planning.

B - A taster allows experience in an area where a trainee has not previously worked..

C - It is a good opportunity to do an audit.

D - It is expensive to do a taster.

E - It is of no use on your CV.

3. Implementing your own taster could be viewed as evidence of what?

A. Commitment to a particular specialty.

B. Future career planning.

C. Personal motivation.

D. Development of a service.

E. All of the above.

4. When considering a structured and useful timetable which one of the following should be incorporated?

A. Follow one consultant's timetable for the entire programme.

B. There is no benefit in meeting other heath care specialists.

C. The majority of the time should be spent on the wards.

D. Have an overall supervisor who will support the process and oversee the timetable, with a named point of contact for each session.

E. There is no need to plan a timetable in advance.

5. Which of the following statements regarding outcomes of a taster are false?

A. It is helpful to feedback regarding the taster so subsequent programmes can be improved.

B. At interview for higher training it is likely that a trainee should demonstrate an interest in, and an understanding of, the specialty applied for.

C. It is a failure of the tasters if the trainee decides that the specialty is not for them.

D. After a taster it is important to reflect on the events and the impact on your career development.

E. Your taster experience may usefully be added to your CV for future jobs.

Answers

1. Answer - E.

If a taster is not running then it is certainly possible to set up your own. A key recommendation of the assessment of the Foundation Programme was to support trainees who would like to do a taster. Liaise with the medical education department and discuss your interest with a consultant.

2. Answer - B.

The aim of a taster is to gain experience in an area a trainee has not previously worked which may aid career choices. Costs should be minimal and covered within the study leave allowance. Although participation in a taster may inspire audit ideas it would be wasted opportunity to spend time on an audit during the taster week. The experience of a taster and the skills learnt could be used to enhance a trainees CV.

DEVELOPING A FOUNDATION TASTER

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3. Answer E.

The primary goal of a taster is to guide career choices. But the skills learnt from organising a taster are varied and can be used to demonstrate development of a service, motivation and commitment to specialty.

4. Answer - D.

A structured timetable should have an overall supervising consultant and a point of contact for each session. It should incorporate varied activities and not be based solely on the wards. Meeting other health care professionals is a key element and aims to develop an understanding of the team you are interested in working in. Planning ahead will ensure a successful placement.

5. Answer: C.

Deciding against a career after a taster is not a negative outcome. It is much better to decide against a specialty prior to embarking on training post. For this reason interviews for higher training assess a candidates interest and understanding of the specialty.

Authors

Dr Jennifer L Kahan
ST3 Oncology
Velindre Cancer Centre
Whitchurch Road
Whitchurch, Cardiff, CF14 2TL
Jennifer.Kahan@wales.nhs.uk

Dr Mick Button
STC Chair, Wales and Consultant Clinical Oncologist
Velindre Cancer Centre
Whitchurch Road
Whitchurch, Cardiff, CF14 2TL

Dr Richard Adams
Consultant Clinical Oncologist
Velindre Cancer Centre
Whitchurch Road
Whitchurch, Cardiff, CF14 2TL
Richard.Adams@wales.nhs.uk

Sr Sam Cox
Velindre Cancer Centre
Whitchurch Road
Whitchurch, Cardiff, CF14 2TL
samantha.cox@wales.nhs.uk

Mrs Angela Voyle-Smith
Education and Development Officer
Velindre Cancer Centre
Whitchurch Road
Whitchurch, Cardiff, CF14 2TL
Angela.Voyle-Smith@wales.nhs.uk

Corresponding Author

Dr Mick Button
Mick.Button@wales.nhs.uk

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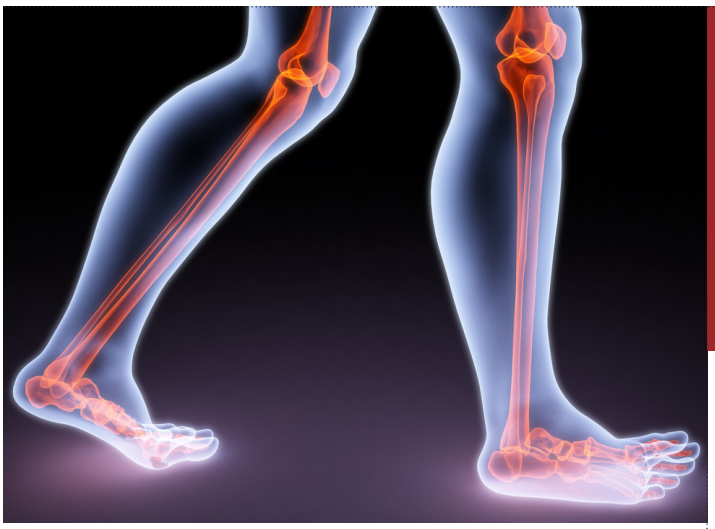
IPILIMUMAB INDUCED COLITIS & PERIPHERAL NEUROPATHY

HEJ Tyrrell, MR Middleton, MJ Payne



Abstract

Cutaneous melanoma is a cancer of the melanocytes found in the basal layer of the skin. Its incidence is rising and risk factors include fair skin, exposure to UV radiation from sunlight or sunbeds, multiple benign pigmented naevi, genetic susceptibility and immunosuppression. (1) Until recently there were few treatment options for metastatic melanoma, responses to chemotherapy being poor, and prognosis was dismal. In recent years new treatments have been developed, such as the BRAF and MEK inhibitors, which are effective in melanomas with a BRAF mutation, and immunotherapies.

The latter stimulate the immune system to fight the cancer; drugs that are currently licensed include the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor Ipilimumab and the PD-1 inhibitors Nivolumab and Pembrolizumab. Ipilimumab has resulted in durable responses in patients with metastatic melanoma, but can result in severe side effects from activation of the immune system against normal tissues.

These drugs are also beginning to be used to treat other types of cancer. We present a case of a man with metastatic melanoma who had severe complications from Ipilimumab treatment. The aim of this case report is to increase awareness of the side effects of immunotherapy and to provide guidance on their initial management.

Ipilimumab Induced Colitis & Peripheral Neuropathyr
Patient Management

Case Report – Presentation and Initial Management

A 65 year old man, normally fit and well, with no major past medical history nor regular medications, presented in December 2013 with a mole on the back of his neck, which was causing him irritation. A shave biopsy unexpectedly showed a 2.8mm Breslow thickness, ulcerated, nodular melanoma. Subsequent wider excision revealed a further 0.3mm melanoma deposit in the subcutaneous fat and one sentinel lymph node from the left side of the neck was positive.

Further neck dissection showed no tumour in 16 lymph nodes resected. A staging CT scan of the chest, abdomen and pelvis identified no metastatic disease and therefore his melanoma was staged as IIIB (T3bN1aM0). He commenced regular surveillance, shared between the oncology and plastics teams.

Just over a year after the initial biopsy a routine surveillance CT scan showed 2 tiny pulmonary nodules of 1mm and 2mm. They were considered to be too small to be diagnostic for recurrence or suitable for biopsy, therefore an interval scan was arranged. This unfortunately showed an increase in nodule size, he had never smoked and it looked atypical for a lung primary radiologically, and therefore this was considered to be metastases from the melanoma. He commenced treatment with Ipilimumab, an immunotherapy treatment which targets CTLA-4.

Ipilimumab - Mechanism of Action & Increased Survival

Immunotherapy treatments stimulate the immune system to fight the cancer. When antigen presenting cells (APCs) present antigens from tumour cells to T-cells this can lead to an immune response. Two signals are required for APCs to activate T-cells: binding of the MHC molecule on the APC to the T-cell receptor, and interaction of B7 on the dendritic cell with CD28 on the T-cell. However, as well as these activating signals there are also known inhibitory signals that can suppress T-cell activation. The alternative binding of B7 on the APC to CTLA-4 on the T-cell surface is one such inhibitory signal (see Figure 1).

IPILIMUMAB INDUCED COLITIS & PERIPHERAL NEUROPATHY

HEJ Tyrrell, MR Middleton, MJ Payne

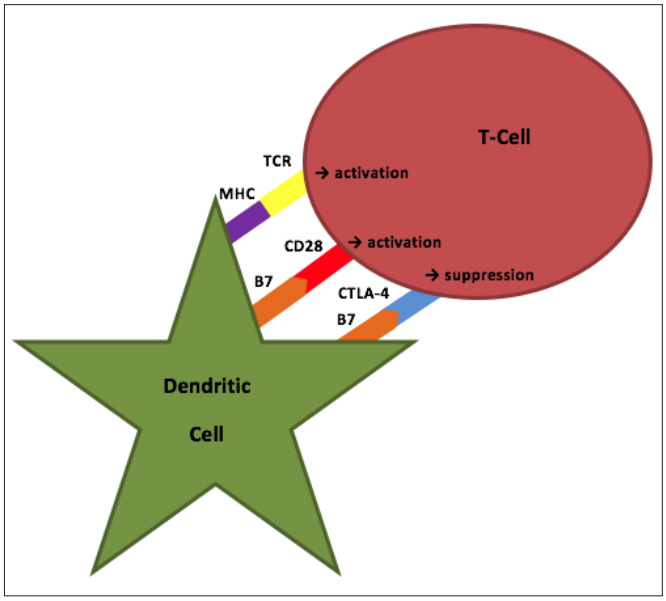


Figure 1: T-cells become activated by MHC on the dendritic cell binding to the T-cell receptor (TCR) on the T-cell and also B7 on the dendritic cell binding CD28 on the T-cell. This activation can be prevented by B7 on the dendritic cell binding to CTLA-4 on the T-cell.

Ipilimumab is a monoclonal antibody targeting CTLA-4, preventing this negative signal and therefore promoting T-cell activation. It 'releases the brakes' on the immune system allowing an immune response against the cancer. (2)

Ipilimumab has been shown to increase survival in patients with metastatic melanoma. For example, in a phase III trial of patients with previously untreated metastatic melanoma or localised unresectable stage 3 melanoma, participants showed a significant increase in overall survival from 9.1 months with chemotherapy alone to 11.2 months with Ipilimumab. (3)

More exciting than the median duration of survival, however, is that a proportion of patients have a long-term durable response with Ipilimumab. The survival curve, showing patient survival against time, plateaus at around 3 years with 22% of patients still alive, and a low incidence of death thereafter. (4)

Case Report – Treatment Complications

Ipilimumab is given intravenously once every 3 weeks for a total of four treatments, each treatment is termed a 'cycle'. On review following his first and second cycles of Ipilimumab treatment, our patient was well with no significant side effects. However, when seen after the third cycle he reported an abnormal sensation in his feet and fingers, which he described as 'like trying to walk on a ship'.

On examination, he had grade 3 neuropathy in his feet, with proprioception particularly affected, and grade 1 sensory neuropathy affecting his fingertips. In view of the neuropathy, Ipilimumab was discontinued, he did not receive the fourth cycle. He was commenced on prednisolone 1mg/kg once daily, with proton pump inhibitor cover.

Grading Toxicity of anti-cancer drug side effects

The National Cancer Institute Common Terminology Criteria for adverse events (CTC criteria), (5) are a standardised way of describing the severity of any side effect of anti-cancer treatments: chemotherapy, immunotherapy, hormonal or targeted treatment. A 'Grade 1' adverse event is mild and may not require treatment, whereas 'Grade 3' is severe, will require the drug in question to be withheld until it resolves, and often results in hospitalisation. 'Grade 4', is a side effect which is life threatening.

Case Report – Treatment Complications (continued)

On review one week later the numbness had improved and he had good fine motor skills in his fingers, but he was still unsteady when walking. However, he had developed a sensation of painful pins and needles in his peripheries. He was given a dose of intravenous methylprednisolone 250mg, the prednisolone was continued, and he was started on gabapentin in addition to simple analgesia.

The neuropathy continued to worsen, so he was prescribed an additional 250mg methylprednisolone , his regular prednisolone was increased to 100mg daily and his gabapentin dose was gradually escalated. Despite this he suffered constant, shooting and stabbing pains in his feet and found that anything touching them, such as the bedding at night, would lead to excruciating pain. He was also struggling to walk around the house.

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He next developed diarrhoea up to three times a day, despite regular loperamide and already being on high dose oral steroids. This led to admission for further methylprednisolone and a flexible sigmoidoscopy. This confirmed a continuous colitis, macroscopically resembling ulcerative colitis, but Ipilimumab induced.

As this occurred despite high dose steroids, he was subsequently prescribed Infliximab as an inpatient. Infliximab is a TNF-α blocker which reduces inflammation, most commonly used to treat autoimmune conditions such as rheumatoid arthritis and inflammatory bowel disease, and is part of the management algorithm for immune checkpoint inhibitor induced colitis. This improved both his diarrhoea and his peripheral neuropathy. A slow wean of his prednisolone was commenced two weeks later.

Ipilimumab – Complications and their Management

As Ipilimumab works by stimulating the immune system, most of the side effects are autoimmune. This is very different from the side effects seen with conventional chemotherapy, which tend to be those of myelosuppression - particularly low white cells resulting in severe infection-, fatigue, and nausea and vomiting. Unlike chemotherapy, the side effects of immunotherapy can present several weeks or even months after treatment is complete.

Ipilimumab treatment can result in inflammation of almost any organ leading to enterocolitis, hepatitis, dermatitis, arthritis, thyroiditis, hypophysitis, neuritis, nephritis and uveitis to name a few. (6) In one trial of Ipilimumab, immune related adverse events were seen in 60% of patients receiving Ipilimumab, and 10-15% had an immune related adverse event of at least grade 3 by CTC criteria. (7) In one phase III trial 36% of patients had to discontinue their Ipilimumab treatment due to the severity of side effects. (3)

As side effects are immune mediated, the initial management is use of steroids, and in many cases this will result in symptom resolution. However, if there is no rapid improvement with steroids, stronger immunosuppressive drugs should be considered. If patients present outside of an oncology centre, the oncology team responsible for the patient should be contacted promptly, so that they can advise on further management. Help may also be sought from specialist teams for the organ system affected.

Immunotherapy for metastatic melanoma is associated with the potential for long-term survival and it is therefore critical that the patient receives the appropriate treatment for immune-mediated toxicities as soon as possible. Giving steroids or stronger immunosuppressants for side effects has not been found to reduce the effectiveness of ipilimumab, with overall survival being similar in patients who did and did not require steroids as a result of this treatment. (8)

One of the most common side effects is colitis, resulting in diarrhoea and abdominal pain. This diagnosis should be considered in any patient currently receiving or who has completed ipilimumab treatment within the preceding 6-8 weeks. Mild diarrhoea, with up to 2 bowel movements above baseline in 24 hours, can be managed symptomatically with loperamide and oral hydration.

However, if stool frequency is greater than this, intravenous fluid and electrolyte replacement should be instigated and steroids started promptly; if the diarrhoea is severe steroids should be given intravenously. Stool samples should be sent for culture and C.difficile testing to rule out infection, and colonoscopy undertaken to confirm the diagnosis and look for ulceration or bleeding.

Colitis can result in perforation, so imaging may be required. If symptoms do not resolve with steroids infliximab should be prescribed, often with guidance from the gastroenterology team, and surgical review is prudent, given the next step for ongoing symptoms is colectomy. (6)

Another complication of ipilimumab is inflammation of the pituitary gland and resulting panhypopituitarism. While this is not one of the most common side effects, it's discussed here as its presentation can be non-specific eg. with fatigue, or life threatening eg. with collapse, requiring a high index of suspicion.

It can also present with pressure effects of pituitary inflammation directly, such as headache, nausea and visual disturbance. If these symptoms develop then hormones such as cortisol, ACTH, TSH and T3/T4 should be measured and an MRI scan of the head can show enlargement of the pituitary and will rule out brain metastases as an alternative cause. These hormonal tests will also help differentiate pituitary dysfunction from adrenal or thyroid gland problems.

If abnormalities are found, discussion is needed with the endocrinology team as, unlike the other side effects of ipilimumab, hypopituitism generally does not resolve and hormone replacement may be required for life. (6)

Discussion

Immunotherapy has had encouraging successes in recent years and has improved the outlook for patients with melanoma. Ipilimumab was the first of these new agents to be licensed, but there are other classes of immunotherapy drug that are now licensed for use, such as the PD-1 inhibitors, and many others currently in clinical trials.

PD-1 inhibitors work in a similar, but slightly different way to Ipilimumab. The PD-1 ligand is expressed by the tumour cell itself, rather than a dendritic cell, and acts on a PD-1 receptor on the T-cell to prevent it activating an immune response.

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The response rates and overall survival with these drugs have been shown to be superior to that of Ipilimumab and there is also a lower frequency of severe side effects, though the nature of complications is similar. CTLA-4 and PD-1 inhibitors have also been trialled in combination, resulting in further improvements in progression free survival and also significant increases in toxicity. (9)

We therefore await definitive information on overall survival to see if widespread use of combination therapy is justified. The PD-1 inhibitors are not only licensed for melanoma, they have also shown activity against non-small cell lung cancer (10,11) and promising activity in trials against renal, head and neck and urothelial tumours. (12,13) It is therefore likely that use of these agents will increase against a range of tumour types.

Conclusion

In summary, Ipilimumab is the first of a class of effective anti-cancer drugs that has opened up a novel way of treating not only melanoma, but also an increasing number of other cancer types. Acute admitting teams outside of the oncology service will soon start to see patients presenting with complications relating to treatment with these drugs; these are very different to those seen with conventional chemotherapy. Knowledge of the likely inflammatory side effects of these treatments and their initial emergency management with steroids and stronger immunosuppression is therefore increasingly important.

Best of 5 MCQs

1. A man receiving Ipilimumab for melanoma presents to the acute medical team with 8 episodes of runny diarrhoea a day and appears dehydrated. What are your first management steps?

a. Prescribe Loperamide and Codeine, discharge with advice to drink lots of fluid, and return if it has not settled in 2 days.
b. Admit, check the FBC to see if he's neutropaenic, send stool cultures, start broad spectrum antibiotics and inform the oncology team of the admission.
c. Admit, send a stool sample for C.difficile toxin, start iv fluids and oral Vancomycin 125mg qds po.
d. Admit, start fluids and electrolyte replacement as appropriate, start steroids and inform the oncology team of the admission.
e. Admit, call the gastroenterology team to request a colonoscopy and commence the patient on Infliximab.

2. How does Ipilimumab work?

a. It stimulates B-cells to produce antibodies against the cancer.
b. It blocks inhibitory signals to the T-cells, therefore allowing them to be activated and produce an immune response against the tumour.
c. It stimulates T-cell receptors, therefore allowing them to be activated and produce an immune response against the tumour.
d. It binds to the tumour cells, therefore resulting in their immune destruction.
e. It binds to dendritic cells, so that they present tumour antigens to the T-cells.

3. Which of the following complications are you more likely to see with Ipilimumab treatment than with conventional chemotherapy?

a. Neutropaenia and severe infections
b. Nausea and vomiting
c. Hypophysitis
d. Peripheral neuropathy
e. Diarrhoea

4. Which is the following is not a risk factor for developing melanoma?

a. Exposure to UV light
b. Genetic susceptibility
c. Smoking
d. Multiple pigmented naevi
e. Immunosuppression

Answers

1. D.

This is probably Ipilimumab induced colitis. Discharging the patient with Loperamide would not be safe with stools of this frequency. He needs to be admitted, receive appropriate resuscitation and commenced on steroids. His treating team need to be made aware of the admission. Sending stool samples for culture and C.diff is sensible, but not the first priority. Infliximab would be the treatment of choice should his symptoms not settle in 48 hours.

2. B.

Ipilimumab blocks CTLA-4, which is a receptor that inhibits T-cell activation. Therefore it promotes T-cell activation.

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3. C.

A and B are more common with conventional chemotherapy than with Ipilimumab. D and E can be caused by Ipilimumab, as in this case report, but are also common with conventional chemotherapy, but due to different mechanisms. C is seen with immunotherapy treatments, but is not seen with conventional chemotherapy.

4. C.

Authors

Mark R Middleton
Consultant in Medical Oncology
Churchill Hospital
Old Road, Headington Oxford, OX3 7LE
mark.middleton@oncology.ox.ac.uk

Miranda J Payne
Consultant in Medical Oncology
Churchill Hospital
Old Road, Headington, Oxford, OX3 7LE
miranda.payne@ouh.nhs.uk

Helen Elizabeth Jane Tyrrell
Registrar in Medical Oncology
Churchill Hospital
Old Road, Headington, Oxford, OX3 7LE

Corresponding Author

Helen Elizabeth Jane Tyrrell
helen_ej_tyrrell@yahoo.com

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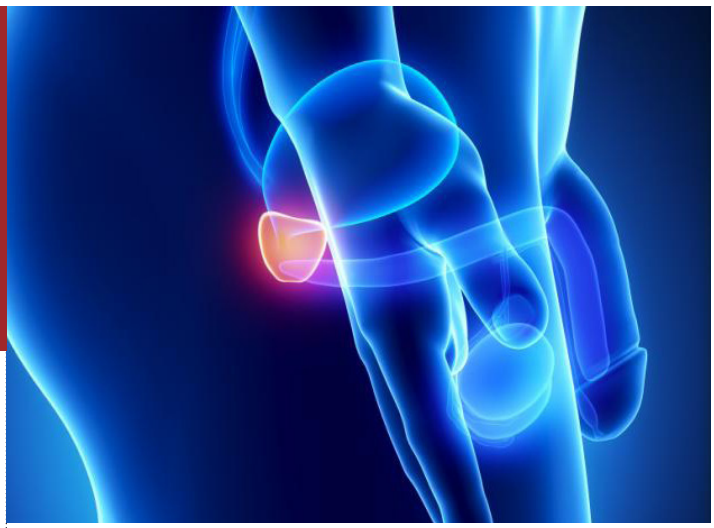
CASE BASED DISCUSSION: MANAGEMENT OF PROSTATE CANCER

J Chan, I Syndikus



Case Based Discussion: Management Of Prostate Cancer
Patient Management

Abstract

Prostate cancer is the most common cancer in men in the UK, with incidence rates increasing 147% since the late 1970s in part due to transurethral resection of the prostate (TURP) procedures and the use of prostate specific antigen (PSA) tests (1). As a result, men admitted acutely into hospital may have a history of prostate cancer and so it is important to be aware of the general principals of treatment.

Most newly diagnosed patients have localised disease where prognosis after definitive treatment is excellent, with almost 85% surviving for five or more years (based on 2010-11 data). Even those with metastatic disease often have survival in the order of years, and advanced prostate cancer can be a chronic disease. We discuss the case of a patient who was initially treated for locally advanced disease, but then had recurrence and is now being managed palliatively for metastatic disease.

Case History

Presentation

A 46 year old gentleman presented to his GP with lower urinary tract symptoms of frequency, nocturia and urgency. Given his young age, the differential diagnosis was more likely to be urinary infection. However, urine dipstick and culture were negative. He subsequently developed worsening obstructive symptoms such as incomplete emptying and weak urinary stream. His International Prostate Symptom Score (IPSS) score was 20.

He had no past medical history and no family history of malignancy. He was not on medication and had no allergies. He lived with his wife and worked as a teacher. He had never smoked and consumed 10 units of alcohol per week. His performance status was 0.

How would you examine him?

On examination, he appeared well, was afebrile and interacting normally. Respiratory, cardiovascular and abdominal examinations were normal. There was no hepatomegaly, lymphadenopathy or lymphoedema. Digital rectal examination found a left-sided irregular and firm nodule in the prostate.

How would you investigate him in the first instance?

Blood tests found that full blood count and biochemical profile were normal, including renal function, liver function tests, and corrected calcium. However his PSA tumour marker was raised at 58 ng/ml (normally less than 3 ng/ml in his age group).

How would you manage him?

He was referred to urology under the 2 week rule, and received a multi-parametric pelvic MRI (Figure 1) followed by trans-rectal ultrasound (TRUS) guided biopsy. Imaging found a T3a N0 staged disease, and histology showed that cores taken bilaterally were extensively infiltrated by adenocarcinoma (Gleason score 4 + 4). As the histopathological findings indicated high risk disease, bone and CT scans were arranged which ruled out overt metastatic disease.

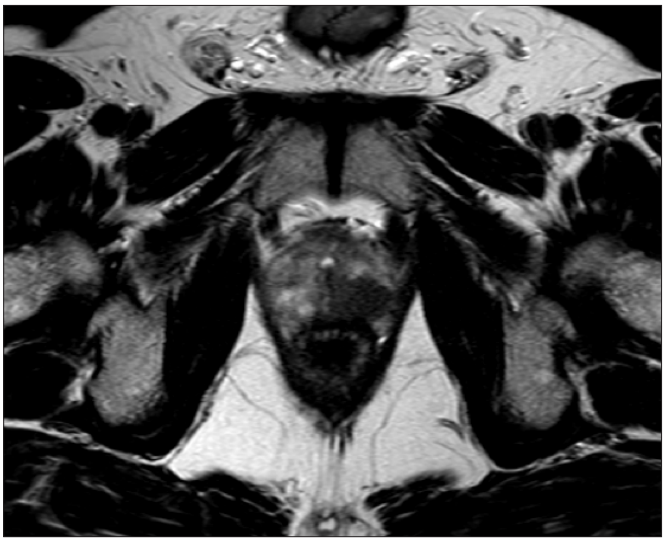


Figure 1: Axial view of T2 weighted MRI of the pelvis, showing cancer as a low signal region in the left posterior aspect of the prostate. As this is a pre-biopsy image, the low signal is not due to haemorrhage.

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For his obstructive urinary symptoms, he was commenced on tamsulosin 400 µg once daily (at night to avoid symptomatic hypotension). He was discussed in the MDT, and surgery was not deemed to be an option due to the high risk locally advanced disease.

Therefore he was reviewed in the clinical oncology clinic together with the urology nurse specialist and a trials nurse specialist. He was offered a combination of hormone therapy and external beam radiotherapy. As with all oncology patients, relevant clinical trials were considered. He was eligible for the 'Systemic Therapy in Advancing and Metastatic Prostate cancer: Evaluation of Drug Efficacy' (STAMPEDE) trial. After discussing the standard treatment (benefits and potential toxicities) and the rationale of the study, he was given relevant information leaflets. A week later, after addressing his outstanding questions, he agreed to the treatment and trial. Informed consent was documented.

He was randomly assigned the control arm within STAMPEDE, and was placed on hormone therapy for a total of 3 years; the patient was sexually active on a regular basis and after discussion, he opted to take bicalutamide 150 mg once daily orally instead of luteinizing hormone-releasing hormone (LHRH) agonist to reduce the risk of erectile dysfunction. He remained fully potent whilst on bicalutamide. After 3 months of hormones, he started his external beam radiotherapy which was 6.5 weeks of treatment as an outpatient.

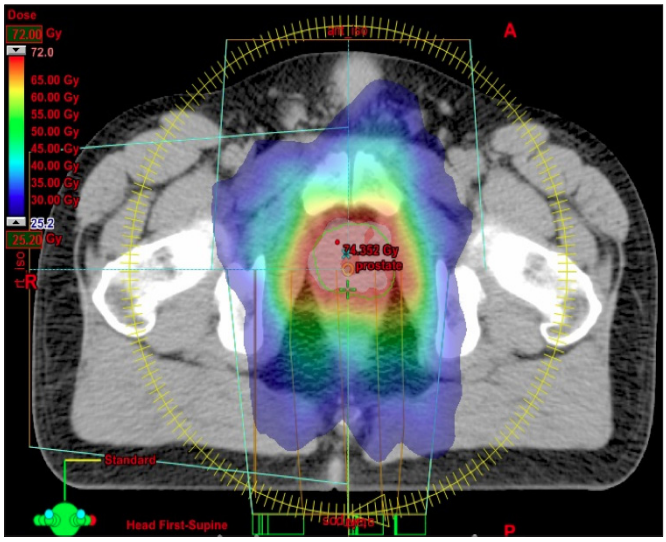

Figure 2: Radiotherapy plan. The patient received 74 Gy in 37 fractions to the prostate and seminal vesicles, as well as 64 Gy to the pelvic lymph nodes, using a rotational IMRT technique.

From the bicalutamide, he developed gynaecomastia associated with breast discomfort. Therefore he was offered 2 sessions of radiotherapy to the breast buds and started tamoxifen 10mg once a week. From the prostate radiotherapy, he experienced more frequent bowel motions but this settled a few weeks after completion of radiotherapy. After 3 years of hormone therapy, his PSA was 0.6 ng/ml, and the bicalutamide was stopped.

However within 3 months, his PSA had risen to 8.2 ng/ml (Figure 3). Given the rapid PSA rise, it was likely due to metastatic disease as opposed to local residual disease, and so hormone therapy was restarted indefinitely. His PSA initially responded but then slowly rose after a year, and he developed left groin pain.

Time point	Intervention
Diagnosis	Started bicalutamide
6 months	Radical radiotherapy to prostate and pelvic lymph nodes
3 years	Stopped bicalutamide
3 years and 3 months	Restarted bicalutamide
4 years and 6 months	Switched bicalutamide to goserelin, palliative radiotherapy to left pubic ramus
5 years	Started a course of docetaxel chemotherapy
6 years	Started abiraterone
7 years	Started dexamethasone and palliative care

Figure 3: Chronological order of management changes.

Re-staging pelvic MRI and bone scan showed a 6 cm diameter bone metastasis in the left pubic ramus (Figure 4). This abutted the adductor muscles anteriorly, and accounted for the pain he experienced when walking.

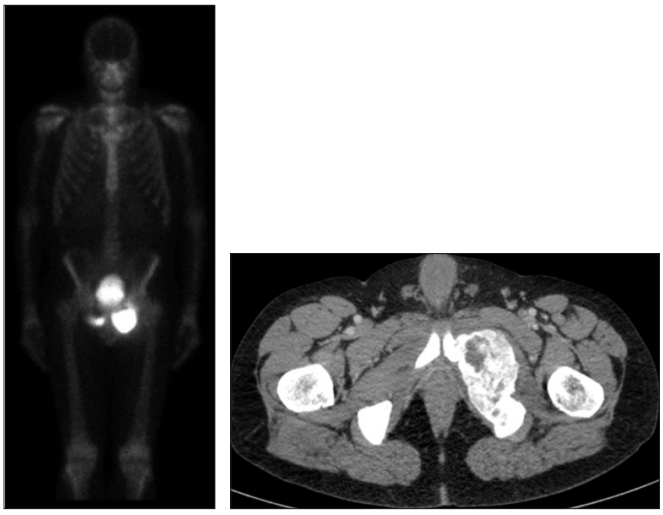

Figure 4: Bone scan (left) and CT (right) showing left pubic ramus recurrence.

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Therefore his bicalutamide was switched to goserelin, and he received palliative radiotherapy to the left pelvis as an outpatient over 1 week. Care was taken to reduce dose overlap to regions previously treated to a radical dose in order to minimise risk of long term toxicity. Again, his PSA responded but began to rise soon after.

Following restaging scans, he received 6 cycles (every 3 weeks) of docetaxel chemotherapy for castrate-resistant prostate cancer (treatment discontinued before the planned 10 cycles due to patient choice). PSA relapse occurred 12 months later, and he received abiraterone with prednisolone to which he responded for 14 months. However on restaging, he had widespread lymph node metastasis and bone metastasis, and his performance status had deteriorated. He was referred to palliative care for continued support and remains on dexamethasone 4mg once daily with proton pump inhibitor (PPI) gastroprotection.

Discussion

Patients diagnosed with prostate cancer can be asymptomatic (identified via an incidental raised PSA) or symptomatic with obstructive symptoms. An IPSS is used to assess urinary symptoms: it consists of 7 symptom questions (concerning incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia) and 1 quality of life question. Haematuria and erectile dysfunction should also be noted.

Constitutional symptoms such as malaise, reduced appetite and weight loss can be present. Specific symptoms and signs from metastasis may include lymph node mass, lymphoedema, bone pain, and fatigue with shortness of breath from anaemia secondary to marrow infiltration. Complications from bone metastasis include pathological fractures and spinal cord compression. Performance status is used to assess fitness and ability to perform daily activities, and can guide decisions about further treatments. In the UK, the Eastern Cooperative Oncology Group (ECOG) score is used most commonly, ranging from 0 (asymptomatic) to 4 (bedbound).

Symptomatic patients may be diagnosed from histology taken following a TURP (1). Histology can also be obtained by TRUS-guided biopsy. The most common pathology is adenocarcinoma which is graded by the Gleason Score, currently ranging from 6 to 10 depending on the observed patterns (2). This grading helps predict prognosis and guide treatment options, and as this patient was Gleason 8 (4+4), he was classified as having high risk disease.

Optimal imaging for staging is a multi-parametric MRI including two functional sequences such as diffusion weighted and dynamic contrast enhanced imaging. European Society of Urogenital Radiology (ESUR) guidelines recommend that imaging should be performed prior to biopsy, as both tumour and haemorrhage can appear as low signal regions on T2 weighted images (3). For this patient, the low signal seen is therefore due to malignant disease. Tumour, lymph node and metastasis (TNM) staging, currently in its seventh edition, is accepted by the Union for International Cancer Control (UICC) (Figure 5). As his disease had extracapsular extension, but not into the seminal vesicles, with no nodal or metastatic disease, the staging was T3a N0 M0.

T1		**Not palpable or visible**
	T1a	≤5%
	T1b	>5%
	T1c	Needle biopsy
T2		**Confined within prostate**
	T2a	≤one-half of one lobe
	T2b	More than one-half of one lobe
	T2c	Both lobes
T3		**Through prostatic capsule**
	T3a	Extracapsular
	T3b	Seminal vesicle(s)
T4		**Fixed or invades adjacent structures: external sphincter, rectum, levator muscles, pelvic wall**
N1		**Regional lymph node(s)**
M1		**Distant metastasis**
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

Figure 5: TNM staging (UICC, seventh edition).

For localised disease, treatment options include conservative management, radical prostatectomy, radiotherapy (external beam radiotherapy or brachytherapy) ± hormone therapy (6 months for intermediate risk disease, 2-3 years for high risk disease). As he has a high risk locally advanced disease, external beam radiotherapy with hormone therapy was suitable.

Those patients managed by surgery are primarily under the care of the urologist, whilst those managed by radiotherapy and hormones are under the clinical oncologists (oncologists who are able to deliver radiotherapy). For prostate cancer, medical oncologists (oncologists who specialise in systemic treatments) are often involved in the context of clinical trials for metastatic disease.

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Toxicity from prostate radiotherapy can be systemic (e.g. fatigue) or localised (e.g. skin soreness, urinary function such as slow flow, frequency and urgency, or bowel function such as diarrhoea and tenesmus). These side effects tend to lag behind the treatment itself. Acute toxicity generally settles with time, but long term effects can occur, such as incontinence, especially if the same area is re-irradiated.

Hormone therapy aims to reduce testosterone function, mainly by luteinising hormone-releasing hormone (LHRH) agonist (e.g. goserelin) or anti-androgens (e.g. bicalutamide). Side effects include fatigue, hot sweats, erectile dysfunction, low mood and weight gain. Bicalutamide is less likely to cause erectile dysfunction but can result in breast tenderness and gynaecomastia. Individual patient preference may depend on the toxicity profiles.

Prognosis following surgery or radiotherapy is broadly similar. From the Conventional or Hypofractionated High dose intensity modulated radiotherapy for Prostate cancer (CHHiP) study, 5 year progression free survival was 88.3% with the widely accepted currently conventional external beam radiotherapy dose schedule of 74 Gy in 37 fractions, and 90.6% with the dose schedule of 60Gy in 20 fractions (4). As a result, 60Gy in 20 fractions will likely be accepted as the standard UK schedule.

After radical treatment, patients can be monitored with serial PSAs, and if there is a biochemical relapse, patients suitable for salvage treatment such as prostatectomy or cryotherapy should have restaging scans. However the former is more complicated following radical radiotherapy, and the latter is not a standard treatment.

For metastatic disease, initial management is hormone manipulation, and in some patients, with the addition of up front docetaxel chemotherapy. Disease is often responsive for 1 - 2 years, after which progression occurs despite primary hormone therapy (castrate-resistant disease). These patients can be treated by further chemotherapy such as cabazitaxel, as well as other treatment options such as abiraterone, enzalutamide and radium 223.

The STAMPEDE study is a large multi-arm multi-stage UK trial running at many centres, with the hypothesis that early use of active therapies may give a larger absolute benefit in overall survival as the primary endpoint (5,6). Most recently, this has shown that docetaxel improves survival for hormone-naïve prostate cancer, and so it is being considered as routine practice for newly diagnosed metastatic patients and some high-risk non-metastatic patients, such as this patient when he initially presented.

Metastatic disease often involves bone, and palliative radiotherapy is a good treatment option. This can be delivered in a single day. Spinal cord compression must always be suspected if the patient has lower limb neurological features and/or urinary/bowel disturbance, and the patient should be on bed rest, started on steroids (such as dexamethasone 8mg twice a day with PPI) and sent for an urgent MRI spine. If confirmed, the patient should be discussed with the neurosurgical and the clinical oncology teams for management such as surgical decompression or palliative radiotherapy.

Conclusion

Prostate cancer is common, and can be slow and indolent. Fit patients with locally advanced disease are suitable for radiotherapy and hormone therapy. However management options should always be discussed with the patient as some may be inappropriate due to multiple comorbidities and poor performance status, where other disease processes are overall more significant than the prostate cancer.

Questions

1)What is an important side effect of tamsulosin?

a. Hair loss
b. Postural hypotension
c. Runny nose
d. Nausea
e. Diarrhoea

2)What is important to do when starting goserelin therapy?

a. Commence patient on prophylactic aspirin
b. Commence s.c. heparin
c. Check testosterone levels
d. Commence bicalutamide for 2 weeks beforehand
e. Commence bicalutamide and goserelin together

3)What is the side effect more associated with bicalutamide than goserelin?

a. Gynaecomastia
b. Itchy skin
c. Erectile dysfunction
d. Weight gain
e. Hot flushes

CASE BASED DISCUSSION: MANAGEMENT OF PROSTATE CANCER

J Chan, I Syndikus

4) Which tumour staging is classed as classified as localised intermediate risk prostate cancer?

a. PSA 5.6ng/ml, clinical stage T1c, Gleason score 3+3
b. PSA 10.6ng/ml, clinical stage T1c, Gleason score 3+4
c. PSA 5.6ng/ml, clinical stage T2c, Gleason score 4+4
d. PSA 25.6ng/ml, clinical stage T1c, Gleason score 3+3
e. PSA 5.6ng/ml, clinical stage T3a, Gleason score 4+3

5) What are the most common sites of metastasis for prostate cancer?

a. Brain and meninges
b. Lung and thyroid
c. Pelvic lymph nodes and bone
d. Liver and kidney
e. Adrenals and pancreas

Teaching Notes

1) Tamsulosin is an alpha-1 selective adrenergic receptor antagonist which relaxes smooth muscle including in the bladder neck, resulting in improved urinary flow. However it can also affect smooth muscle in the vasculature, leading to hypotension and dizziness.

2) Goserelin is a gonadotrophin-releasing hormone analogue, and works by down-regulating the receptors, leading to reduced FSH and LH, and ultimately inhibit androgen and oestrogen production. However as an analogue, there is an initial phase of stimulation that can potentially cause a tumour flare, and it is recommended to use a concomitant anti-androgen such as bicalutamide (at least 3 days before goserelin administration and continue for around 3 weeks).

3) Bicalutamide has a higher risk of causing gynaecomastia and breast tenderness than goserelin, but has a lower risk of erectile dysfunction.

4) Gleason score of 6 (3+3) is classified as low risk, 7 (3+4 or 4+3) as intermediate risk, and ≥8 as high risk. PSA <10 ng/ml is low risk, 10 – 20 ng/ml is intermediate risk, and >20 ng/ml is high risk. T1-T2a is low risk, T2b is intermediate risk, and ≥T2c is high risk. Localised prostate cancer is <T3.

5) Metastatic prostate cancer most frequently involves lymph node and bone metastasis, and hence spinal cord compression should be suspected in patients with lower limb neurological features and/or urinary/bowel disturbance.

Authors

Isabel Syndikus
Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Road, Bebington, Wirral, CH63 4JY
Isabel.syndikus@clatterbridgecc.nhs.uk

Joachim Chan
Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Road, Bebington, Wirral, CH63 4JY

Corresponding Author

Joachim Chan
Joachim.chan@clatterbridgecc.nhs.uk

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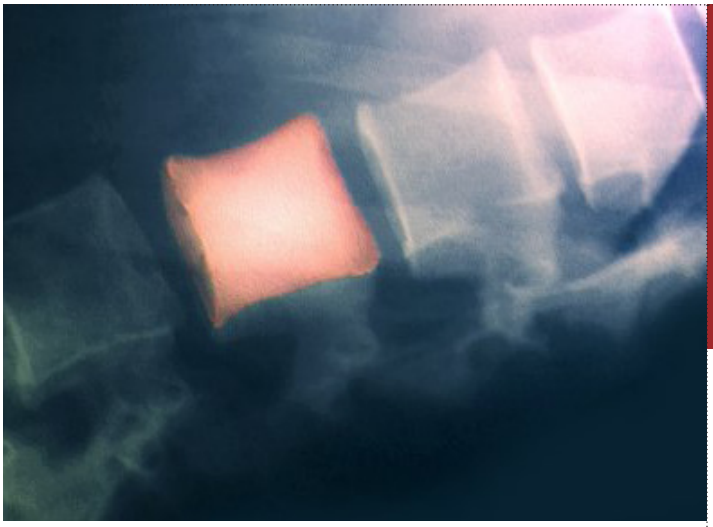
MANAGING A PATIENT WITH METASTATIC SPINAL CORD COMPRESSION

HJ Ching, V Wood, M Bayne



Managing A Patient With Metastatic Spinal Cord Compression
Patient Management

Abstract

Metastatic spinal cord compression (MSCC) is an oncological emergency. We present a previously fit and well 74 year old gentleman that presented with MSCC secondary to diffuse Large B-Cell Lymphoma (DLBCL). He was treated with palliative radiotherapy. We will be emphasising the principle management of individuals with MSCC as their first manifestation of an unknown primary malignancy.

Curriculum

2 Relationship and communication with patients

2.1 Treats the patient as the centre of care within a consultation

2.2 Communication with patients

2.3 Communication in difficult circumstances

7 Good clinical care

7.3 History and examination

7.4 Diagnosis and clinical decision-making

8 Recognition and management of the acutely ill patient

8.4 Manages pain

Case History

Mr JB, a 74 year old gentleman with no significant past medical history, presented to the emergency department with back pain and lower limbs weakness. He has been reporting an on-going back pain for several months, and the reason he was brought into hospital was the development of a new left lower limb weakness. Clinical examination revealed weakness in his left lower limb with increased numbness on the affected limbs. However, no loss of sensation was found. He reports normal bowel and bladder function, and no 'saddle' paraesthesia was identified.

An urgent whole spine magnetic resonance imaging (MRI) was organised, and this confirms MSCC. An extradural mass was seen at T2 and T3 vertebral level, extending through the intervertebral foramina into the canal. Similar appearances were seen at T4 vertebral level where the spinal cord is flattened, distorted and was surrounded by abnormal soft tissue, compressing on the spinal cord. Furthermore, more disease was seen at T6 and T7 vertebral body, causing cord compression. His case was discussed with the regional neurosurgical team. Unfortunately, he was not a suitable candidate for surgical intervention due to the multiple level of disease involvement.

An urgent CT staging scan was requested and this revealed disseminated malignancy, likely to be lymphoma. We managed to organise an urgent CT-guided biopsy of the paravertebral mass on the same day. The final histology from the biopsy confirmed germinal cell phenotype DLBCL. After he had his biopsy, high dose corticosteroids, dexamethasone 16mg was started. He received palliative radiotherapy to the affected area later that evening, 20Gy in 5 fractions over 5 days. He reports that his pain has improved after taking corticosteroids the following day. He continues to mobilise, and was assessed by the physiotherapist and discharged home after he completed his radiotherapy.

His case was discussed in the haematology multidisciplinary team (MDT) meeting. He was started on R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy once the diagnosis of DLBCL was confirmed. Six-months later, he completed six cycles of R-CHOP with two doses of prophylactic intrathecal methotrexate. The post treatment positron emission tomography (PET) scan showed a good response to treatment with residual disease and uptake in left paraortic nodal tissue.

MANAGING A PATIENT WITH METASTATIC SPINAL CORD COMPRESSION

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He was then referred to the clinical oncological team for consolidative radiotherapy to this area. Unfortunately, his disease relapses four months later and he received salvage ifosfamide-VP16213-methotrexate (IMVP-16) chemotherapy. Three-months later, his PET scan confirmed complete metabolic remission. He was last seen in September 2015 (eighteen-months since he had his last treatment) and he continues to remains in complete remission. He continues to mobilise independently, and carry on living an active lifestyle.

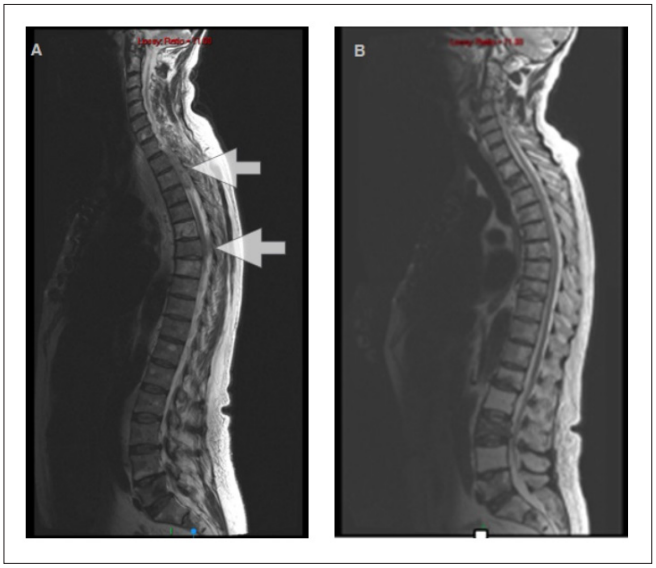

Figure 1: Mr JB's MRI of the whole spine taken a year apart. A: MRI at presentation showing cord compression at two levels as depicted by the arrows. B: MRI of the whole spine performed 12 months later revealed background osteoporotic changes only.

Discussion

This is most common in patients with breast, prostate and lung carcinoma. MSCC develops when there is direct tumour invasion resulting in direct compression or as consequence of a pathological vertebral body collapse impinging against the spinal cord or cauda equina.

MSCC can cause an array of symptoms. Pain is one of the common presenting symptoms of MSCC. As a clinician, it is often difficult to distinguish between benign musculoskeletal back pain with pain secondary to bony metastases. Back pain that is associated with abnormal neurological findings should warrant further investigations.

Additionally, one of the earlier symptoms of MSCC that patients often report is paraesthesia, or change of sensation distal to the level of compression. It is also identified that the severity of bladder dysfunction is directly proportional to the severity of motor dysfunction (2).

SINS Component		Score
Location	Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
	Mobile Spine (C3-C6, L2-L4)	2
	Semi rigid (T3-T10)	1
	Rigid (S2-S5)	0
Pain	Yes	3
	Occasional pain but not mechanical	1
	Pain-free lesion	0
Bone Lesion	Lytic	2
	Mixed lytic/blastic	1
	Blastic	0
Radiographic spinal alignment	Subluxation/translation present	4
	De novo deformity (kyphosis/scoliosis)	2
	Normal alignment	0
Vertebral body collapse	>50% collapse	3
	<50% collapse	2
	No collapse but with >50% body involved	1
	None of the above	0
Posterolateral involvement of spinal elements	Bilateral	3
	Unilateral	1
	None of the above	0

Table 1: Spinal Instability Neoplastic Score. A score of 0 to 6 suggests stability; 7 to 12 suggests indeterminate stability and 13 to 18 suggests instability. [Adapted from reference 3]

Another area of controversy is patient's mobility following the diagnosis of MSCC. Historically, mobilisation is usually only allowed after radiotherapy or after surgical decompression with spinal stabilisation. However, there is no clinical or research evidence to support these. It has been suggested that severe mechanical pain (pain made worse with spinal movement, lifting objects and standing) is highly indicative of spinal instability (2).

If a clinician is concern about spinal instability, the patient should be nursed lying flat with a neutral spine alignment until stability of the spine is achieved, usually by an external brace or following a surgical intervention in selected cases. The spinal instability neoplastic score (SINS) is a scoring system which helps guide a clinician to decide whether a patient has a stable or unstable spine. In this case scenario, Mr JB scored 6 out of 18, and his spine was deemed stable. This should always be taken in context with the patient's clinical symptoms. It is recommended that any patient with a score of more than 7 should have a discussion with the neurosurgical team (3).

The gold standard imaging modality is an MRI of the whole spine. The whole spine should be imaged after a study revealed that approximately 20% of MSCC presented with more than one level of compression as shown in this patient's case (4). Furthermore, an MRI also provides further vital information about the presence of bone marrow involvement, or any association with paravertebral soft tissue masses.

MANAGING A PATIENT WITH METASTATIC SPINAL CORD COMPRESSION

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If an MRI is contraindicated, the next best imaging modality would be a CT imaging of the whole spine. A CT image may raise suspicion of a potential spinal cord compression. However, it does not define the cerebrospinal fluid (CSF) space that surrounds the spinal cord, which is easily visualised with an MRI. The National Institute of Care Excellence (NICE) has recommended that all patients with suspected MSCC should have an MRI within 24 hours of presentation (5).

According to a study by Quraishi et al., the incidence of MSCC from an unknown primary was found to be 6% (6). Although the study's postoperative outcomes were not too dissimilar in known primary and unknown primary, the underlying tissue subtype is helpful to predict prognosis (see table 3). If the patient with MSCC of unknown primary undergoes surgery, it is then possible to have a histological diagnosis. In most cases, where surgery is not indicated, it can be proven to be a challenge trying to identify the underlying malignancy.

A cross-sectional CT imaging is often performed to try to identify the primary cancer as well as to stage the extent of the disease. In this case, Mr JB was found to have wide spread disease with generalised lymphadenopathy and a paravertebral mass, probably lymphoma. In addition to cross sectional CT imaging, a panel of tumour markers is often sent, to help narrow down the search for a potential primary malignancy. In this case, Mr JB's tumour markers were found to be unremarkable.

Tumour markers	Associated malignancies
Alpha fetoprotein (AFP)	Nonseminomatous germ cell tumour, hepatocellular carcinoma
CA15-3	breast cancer
CA 19-9	Predominantly pancreatic cancer, can be raised in colorectal carcinoma
CA 12-5	Predominantly ovarian cancer, can be raised in other gynaecological cancer including endometrial cancer, fallopian tube cancer
Carcinoembryogenic antigen (CEA)	gastrointestinal cancer, cervical cancer, ovarian cancer, medullary thyroid carcinoma
Prostate specific antigen (PSA)	Prostatic carcinoma
β-human chorionic gonadotropin (β-hCG)	gestational trophoblastic disease, germ cell tumour, choriocarcinoma, bladder cancers

Table 2: List of common tumour markers currently in clinical practice.

At this point in time, we have established that Mr JB has a widespread disease likely to be lymphoma causing MSCC. However, no histological diagnosis has been made yet. The clinical dilemma is whether to commence Mr JB on high dose corticosteroids. If this is lymphoma, corticosteroids may affect tissue diagnosis, as lymphoma is very sensitive to corticosteroids and may regress with it.

An urgent CT-guided biopsy of the paravertebral mass was organised on the same day, hence we were able to delay starting Mr JB on steroids after the biopsy. Corticosteroids, usually dexamethasone are given to patients who have suspected MSCC as it may help to improve the oedema around the spinal cord and shrink tumour bulk. Therefore, this can also help alleviate the patient's pain. A loading dose of dexamethasone 16mg is given as soon as there is clinical suspicion of an underlying MSCC.

This would be continued during the course of radiotherapy or while awaiting surgery. The dose could be reduced gradually over several days, with the aim of stopping it completely upon completion of radiotherapy, or after surgery. It is highly recommended that a proton pump inhibitor, histamine-2 blockers or antacid be given alongside corticosteroids, due to the gastro-intestinal side effects.

Characteristics		Score
Performance status	Poor (PS 10-40%)	0
	Moderate (PS 50-70%)	1
	Good (PS 80-100%)	2
Number of extra spinal bone metastases foci	3 or more	0
	1 -2	1
	0	2
Metastases to the major internal organs	Unresectable	0
	Resectable	1
	No metastases	2
Primary site of cancer	Lung, osteosarcoma, stomach, bladder, oesophagus, pancreas	0
	Liver, gallbladder, unidentified	1
	Others	2
	Kidney, uterus	3
	Rectum	4
	Thyroid, prostate, breast, carcinoid tumour	5
Palsy	Complete	0
	Incomplete	1
	None	2

Table 3: Tokuhashi scoring system for preoperative prognostic assessment of metastatic spinal disease. A total score of 12 - 15, prognosis is one year or more; a total score of 9-11, prognosis is six months or more; total score of 0-8, prognosis is less than six months.[Adapted from reference 7]

Surgical intervention is deemed to be the definitive treatment for MSCC. The Tokuhashi prognostic score is often used to select cases appropriate for surgical intervention (7). The benefits of performing surgery in MSCC are allowing decompression of the spinal cord, and providing spinal stability, which will help in alleviating the patient's pain.

MANAGING A PATIENT WITH METASTATIC SPINAL CORD COMPRESSION

HJ Ching, V Wood, M Bayne

If the patient is not known to have an underlying cancer diagnosis, surgery will provide tissue sample for histological diagnosis. If a patient develops paraplegia as a consequence of MSCC, surgery does not reverse this. However, surgery in this group of patients may help palliate their pain. However, in order to warrant a surgical intervention, a patient needs to be fit for anaesthesia, and they would need to have a relative good prognosis from their underlying malignancy.

The majority of patients with MSCC would not be candidates for surgery. Radiotherapy provides a non-invasive treatment modality for patients who have pain, and even those who are in complete paraplegia for more than 24 hours.

Radiotherapy does not improve the structural instability, and therefore those who are deemed to have an unstable spine, but who are unsuitable for surgery, would require an external brace indefinitely. Pre-operative radiotherapy is not recommended but post-operative fractionated radiotherapy should be considered for patients with a good prognosis from their underlying malignancy to reduce local recurrence.

In conclusion, MSCC is not an uncommon complication of patients with metastatic disease involving the vertebral bodies. A coordinated MDT approach is important if a patient presents with MSCC from an unknown primary malignancy. Special thought needs to be considered prior to starting corticosteroids in MSCC if an underlying haematological malignancy were one of the differential diagnoses. The definitive treatment for MSCC is surgical intervention; however, this is only performed in selected cases. In this scenario, radiotherapy did preserve and improve Mr JB's neurological function, as well as palliate his pain.

Test Yourself

Question 1: Which one of the following is false?

A. Spinal surgery is indicated in patient with metastatic spinal cord compression

B. The primary tumour is relevant to the management of the cord compression

C. Thoracic vertebrae are the most commonly affected

D. Spinal cord compression in malignancy is always the result of vertebral metastases

E. A sensory level does not accurately indicates the level of metastatic involvement

Question 2: With regards to medical treatment in suspected MSCC, which of the following is false?

A. Hyperglycaemia, insomnia, mania and dyspepsia may all be caused by high dose steroids

B. In the absence of neurological signs, steroids should be continued until imaging has taken place

C. Dexamethasone 16mg IV should be given

D. Low molecular weight heparin is not contraindicated

E. If no evidence of metastatic spinal cord compression is seen on scan, steroid dose should be reduced slowly before stopping

Answers

1. Answers: D

Spinal metastatic disease is the most common cause of cord compression. However, cord compression can also be caused by primary tumours or secondary deposit arising close to the cord.

Thoracic vertebrae are the most common sites to be affected by metastatic disease and therefore the most likely site for MSCC.

Histological diagnosis of the primary tumour is relevant as this will help guide further management as well as patient's prognosis.

Spinal surgery is the definitive treatment for patient with MSCC. However, surgery will only applies to a selected few only.

Imaging will often show metastatic involvement at levels different to and beyond those suspected on clinical examination. As a consequent, the whole spine should be imaged, even though the signs are confined to a specific area of the spine.

MANAGING A PATIENT WITH METASTATIC SPINAL CORD COMPRESSION

HJ Ching, V Wood, M Bayne

2. Answers: E

The use of high dose steroids may result in numerous side effects mainly dyspepsia, insomnia, and hyperglycaemia. There is increased morbidity with long term use of steroids as it increases the risk of osteoporosis, thinning of the skin, and immunosuppression. Dexamethasone 16mg can be given either intravenously or via the oral route.

Low molecular weight heparin is not contraindicated as majority of patients with MSCC have reduced mobility. Given they have an underlying cancer diagnosis, this will put them at higher risk of developing venous thromboembolic events.

Corticosteroids should be commenced if MSCC is suspected. If the MRI performed did not reveal any evidence MSCC, corticosteroids can be stopped without the need of reducing the dose.

Authors

Heng Jeng Ching
ST5 Clinical Oncology
Poole Hospital NHS Trust
Longfleet Road
Poole
Dorset
BH15 2JB

Victoria Wood
ST6 Clinical Oncology
Poole Hospital NHS Trust
Longfleet Road Poole
Dorset
BH15 2JB
victoria.wood@poole.nhs.uk

Mike Bayne
Consultant Clinical Oncology
Poole Hospital NHS Trust
Longfleet Road
Poole
Dorset
BH15 2JB
mike.bayne@poole.nhs.uk

Corresponding Author

Heng Jeng Ching
hjengching@doctors.org.uk

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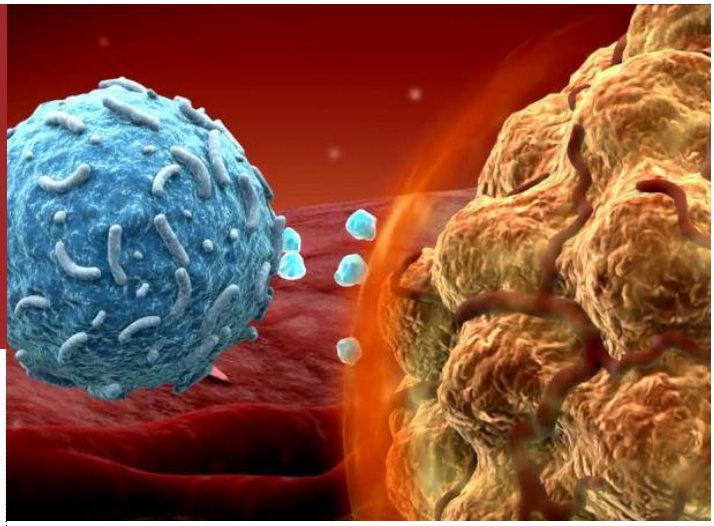
NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY A NEW TREATMENT MODALITY

C O'Hanlon Brown, J Waters, R Shah



Non-Small Cell Lung Cancer - Immunotherapy A New Treatment Modality
Patient Management

Introduction – Treatment Of Advanced Non Small Cell Lung Cancer

Advanced squamous non-small cell lung cancer (NSCLCa) has a poor prognosis with median survival less than one year. First and second line chemotherapy has proven benefit but following this options are limited particularly for squamous NSCLCa. Immune checkpoint inhibition is a novel approach to cancer treatment, which has recently been proven to have clinical activity in squamous NSCLCa.

Case Study – Response To Immunotherapy In Squamous Nsclca

A 49 year old male was diagnosed with T3N3M1a squamous NSCLCa. He was initially treated with first line chemotherapy – Cisplatin/Vinorelbine with partial response. Within two months of completing chemotherapy his disease progressed rapidly such that he was becoming unfit for further chemotherapy. At that time Nivoloumab, a Program death-1 (PD-1) inhibitor was licensed for use and he was commenced on treatment. He experienced a dramatic clinical and radiological response to treatment and continues to do so.

Discussion – Immunotherapy MOA & Toxicities

Checkpoint inhibition is a novel strategy to harness the immune system to target cancer. Program death-1 (PD-1) is a cell surface receptor whose activation inhibits T-cell response. Monoclonal antibodies that target and inhibit PD-1 have been developed – Pembrolizumab and Nivolumab. PD-1 inhibition releases 'the checkpoint break' on immune response to target tumour antigens ultimately leading to destruction of cancer cells. Checkpoint inhibitors have demonstrated benefit for patients with multiple solid tumours including NSCLCa.

The side effect profile of checkpoint inhibitors is unlike that of cytotoxic chemotherapy or small molecule targeted therapies. As their mechanism of action is to activate the immune response, checkpoint inhibitors cause off target autoimmune reactions which can be severe. Checkpoint inhibitors represent a new and exciting treatment modality for this difficult to treat cancer and are providing long-term clinical benefit to patients. As experience using these novel therapies increases so does the ability to recognise and manage toxicities.

Non-Small Cell Lung Cancer - Immunotherapy A New Treatment Modality

Case study

A 49year old man presented to his GP with a history of progressive hoarseness that had slowly worsened over a six week period. On questioning his GP established he had a 30pack year smoking history. He was referred to an ENT surgeon for further investigation. A nasendoscopy showed a paralysed left vocal cord. A CT scan was therefore arranged and this identified extensive bilateral mediastinal adenopathy, bilateral lung nodules and bilateral supraclavicular adenopathy. A biopsy of the enlarged supraclavicular node diagnosed a squamous non-small cell lung cancer. His cancer was staged as T3N3M1a.

The extent of disease meant that neither surgical resection nor radical chemo/radiotherapy would be feasible. The patient was clinically well and therefore commenced palliative treatment using the chemotherapy regimen Cisplatin/Vinorelbine. A good partial response was achieved after 6 cycles of treatment. Unfortunately just two months after stopping treatment the patient presented with worsening pain, dyspnoea and rapid enlargement of his neck mass.

The standard treatment approach would be treatment with second line chemotherapy – Docetaxel or to consider a clinical trial. However the patients' condition began to rapidly deteriorate. It was felt he was unfit for a clinical trial and of borderline fitness for further chemotherapy. Fortuitously Nivolumab (an anti-PD-1 monoclonal antibody) was licensed for clinical use following the recent publication of a trial demonstrating its efficacy. The trial evidence suggested Nivolumab was less toxic than Docetaxel chemotherapy, so with the patient's consent he commenced Nivolumab treatment. Following just three fortnightly doses the patients clinical deterioration was halted and in fact his symptoms began to improve. CT scans showed a dramatic improvement (Figure 1).

NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY A NEW TREATMENT MODALITY

C O'Hanlon Brown, J Waters, R Shah

He continues on treatment eight months later and is well, fully active and has minimal symptoms. As yet he has not developed any significant side effects on treatment.

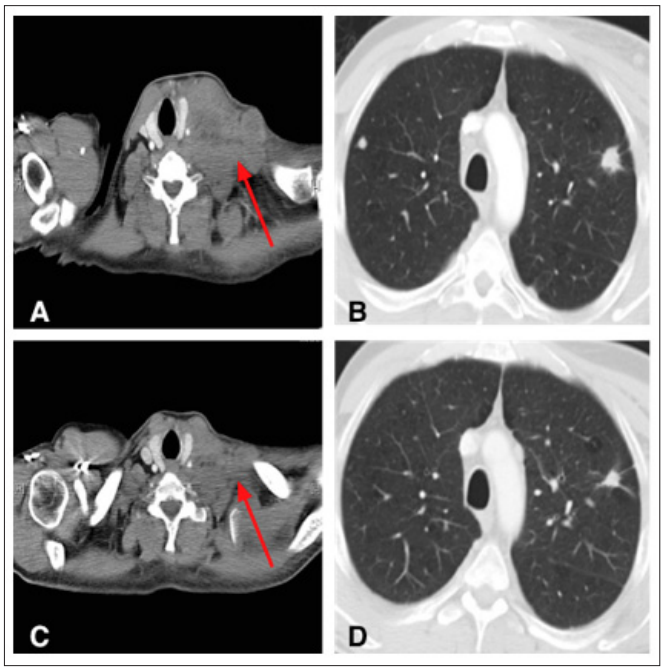


Figure 1: CT scan of patient with squamous non-small cell lung cancer. A and B. CT scan prior to commencing treatment with Nivolumab. Cross sectional imaging of A. neck and B. lung C and D CT scan following one month of Nivolumab treatment demonstrating response to treatment. Cross sectional imaging of C. neck and D. lung.

Non-Small Cell Lung Cancer

Lung cancers can be divided into small cell lung cancer (10-15%), Non-small cell lung cancer (NSCLCa) (85%) and carcinoid tumours (1%). In turn NSCLCa is divided into adenocarcinoma (40%), squamous cell carcinoma (35%) and large-cell carcinoma (10%). In the last 10 years much has been learnt about the molecular pathology of adenocarcinoma of the lung. It is now understood that lung cancers histologically classified as adenocarcinoma, in fact represent a group of lung cancers, with different molecular biology and clinical behaviour.

A steadily increasing number of driver mutations have been indentified including EGFR, Alk, Ras, ROS-1 and Met whose presence defines these different subgroups of lung adenocarcinomas (1). For squamous cell carcinomas, however, the same advances in understanding the molecular biology and its translation into targeted treatment, has not occurred.

Treatment for advanced disease

The mainstay of treatment for advanced/metastatic NSCLCa is cytotoxic chemotherapy. Without treatment median survival with advanced NSCLCa is 3-5mths. Platinum based doublet chemotherapy increases median overall survival to 8-10 months (2,3). On disease progression options for treatment include further second line chemotherapy, which has modest response rates and significant toxicity (5).

Other options include clinical trials or supportive care. Molecular targeted therapies have been demonstrated to have clinical benefit over and above chemotherapy for EGFR mutant cancer and tumours with Alk translocations (4,5). Unfortunately for squamous lung cancers treatment options have remained confined to cytotoxic chemotherapy (2,6).

Immunotherapy and Cancer

It has long been recognised that the immune system plays a role in cancer. In melanoma and renal cell cancer immune therapies e.g interleukin-2 and interferon have been used with clinical benefit (7–9). Unfortunately these treatments demonstrate benefit for a relatively small proportion of patients at a cost of significant toxicity. The CTLA-4 (Cytotoxic T Lymphocyte-associated antigen-4) inhibitor Ipilimumab was the first of a new wave of immunotherapy, termed checkpoint inhibitors to be licensed.

Ipilimumab is a monoclonal antibody that binds and inhibits CTLA-4. CTLA-4 is a T-cell surface receptor which, when active suppresses the T-cell response. Ipilimumab binds CTLA-4 and inhibits down stream signaling. By switching off CTLA-4s inhibitory signal ipilimumab activates the T-cell immune response. The immune system is recruited to target and kill tumour cells. Ipilimumab has proven activity in the treatment of advanced malignant melanoma (10).

Programmed death-1 (PD-1) receptors and their ligands PD-L1 and -L2 are inhibitory cell surface molecules that negatively regulate T-cell activation. PD-1 is expressed on the surface of effector T-cells. It binds its ligands PD-L1 and -L2 expressed on the surface of antigen presenting cells (Figure 2). Two PD-1 inhibitors have been developed and are currently in use in the clinic – Pembrolizumab and Nivolumab. Anti-PD-L1 antibodies are also in clinical trials. Anti-PD-1 antibodies bind to and inhibit PD-1 signaling which leads to increased T-cell activation. Targeting PD-1/PD-L1 has demonstrated activity in multiple solid tumours including melanoma, renal cell tumours and Non-small cell lung cancer (11,12).

NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY A NEW TREATMENT MODALITY

C O'Hanlon Brown, J Waters, R Shah

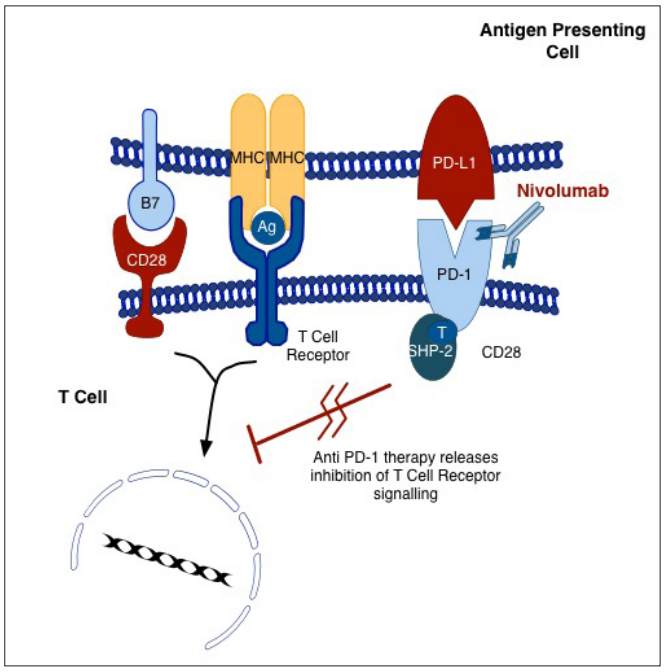


Figure 2: The immune synapse. The monoclonal antibody Nivolumab binds to PD-1 on the surface of T-cells. It acts to suppress PD-1/PD-L1 mediated inhibition of T-cell activation. PD-1 programmed death-1, PD-L1 programmed death ligand -1, MHC - Major Histocompatibility Complex, Ag – antigen SHP-2 - SH2-containing tyrosine phosphatase 2

Efficacy in Non-small cell lung cancer

A phase III clinical trial in advanced squamous NSCLCa compared Docetaxel, the standard of care second line cytotoxic drug, with Nivolumab (13). The response rate for those treated with Nivolumab was 20% compared to 9% for those treated with Docetaxel. Progression free survival at one year was 21% compared to 6%, favouring Nivolumab therapy (p=0.008).

Overall survival was also improved – 9 months versus 6 months (HR 0.59 p<0.0001). On average patients in this study who responded to Nivolumab did so within the first two months of treatment but there were some late responders. The median duration of response was not reached in the Nivolumab arm, which suggests that for those who do respond the response is sustained.

Immune toxicity

Anti-PD-1 therapies are for the most part well tolerated. The most common toxicities are mild to moderate fatigue, anorexia, nausea and diarrhea. In clinical trials the rates of fatigue on treatment was 16% compared to 33% with Docetaxel. Checkpoint inhibitors do not target cell division therefore they do not cause the side effects frequently associated with cytotoxic chemotherapy including vomiting, neutropaenia and hair loss. By activating the immune system check point inhibitors cause off target auto-immune responses (immune related Adverse Events - irAEs) of a wide variety, including colitis, hepatitis, nephritis, pneumonitis, thyroid dysfunction, endocrinopathies – including hypophysitis and skin rash (14).

Early recognition and prompt treatment with corticosteroids are the cornerstones of management of irAEs. For patients with mild to moderate symptoms oral prednisolone 0.5-1mg/kg should be instituted and weaned slowly over a month if symptoms improve. Patients with severe toxicity should receive intravenous steroids – 1mg/kg IV methylprednisolone. Higher doses may be required to treat severe pneumonitis. Infliximab has been used to good effect for patients with severe auto-immune colitis not responding to steroids within 5-7 days (15,16).

Endocrinopathies should be managed with appropriate replacement therapy and consider investigation for hypophysitis as its presentation is often insidious. Topical steroids can be for used to manage rash covering <30% of body together with anti-histamine for pruritis. For reactions refractory to steroids immuno-suppressants eg mycophenalate should be considered. Early input from the appropriate medical specialist for patients with severe toxicity is recommended. For each system protocols are evolving for management of irAEs as experience grows.

Future questions

Studies are seeking to identify a biomarker for response to allow selection of patients most likely to obtain benefit from treatment. PD-L1 expression has been examined in a number of trials as a possible biomarker and shows potential. As the drugs themselves do not cause direct effect on the tumour there have been cases in trials where patients had ongoing responses following treatment discontinuation, which poses questions about how long the drugs need to be given. The sequencing of the use of immunotherapy and chemotherapy in the management of NSCLCa with respect to maximizing benefit is also of interest to researchers.

NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY A NEW TREATMENT MODALITY

C O'Hanlon Brown, J Waters, R Shah

Conclusion

Advanced/metastatic NSCLCa is a common cancer with a poor prognosis. Despite advances in molecular therapy for adenocarcinomas of the lung, cytotoxic chemotherapy remains the mainstay of treatment for squamous cell carcinomas. The discovery of a role for immunotherapy in the treatment of advanced squamous NSCLCa is therefore an exciting advance that offers great hope to patients. Much remains to be learned about how best to harness immunotherapy to achieve maximal clinical gain for patients but also to manage toxicity. As these drugs move to more widespread clinical use it is imperative that clinical staff across a range of specialties become familiar with their side effect profile and management of toxicities.

Questions

1. Which of the following monoclonal antibodies targets CTLA-4?

1. Pembrolizumab

2. Nivolumab

3. Bevacizumab

4. Ipilimumab

5. Trastuzumab

2. Common side effects associated with cytotoxic chemotherapy includes –

1. Pneumonitis

2. Neutropaenia

3. Squamous cell carcinomas

4. Hypertension

5. Colitis

3. Common side effects associated with checkpoint inhibitors include –

1. Nausea/vomiting

2. Hairloss

3. Neutropaenia

4. Colitis

5. Thrombocytopaenia

4. A patient with a known diagnosis of Non-small cell lung cancer presents to A&E with severe diarrhea – passing bowel motions 6x/day. The patient's wife reports he has been receiving nivolumab treatment for two months. What is the most appropriate treatment?

1. Loperamide

2. IV prednisolone

3. Infliximab

4. Oral Prednisolone

5. Codeine

Answers

1. Answer 4.

Pembrolizumab and Nivolumab are both anti-PD-1 monoclonal antibodies. Bevacizumab is a monoclonal antibody that binds the pro-angiogenic growth factor VEGF (vascular endothelial growth factor). Trastuzumab or Herceptin is a monoclonal antibody that targets Her-2 a cell surface growth receptor. Trastuzumab is used in breast cancer and gastric cancer.

2. Answer 2.

The most common side effects of cytotoxic chemotherapy are fatigue, nausea/vomiting, neutropaenia, hair loss, and diarrhea/constipation. The other listed side effects are associated with different targeted therapies.

NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY A NEW TREATMENT MODALITY

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3. Answer 4.

The most common side effects associated with checkpoint inhibitors are colitis and hypothyroidism. The other listed side effects are associated with cytotoxic chemotherapy.

4. Answer 4.

Colitis occurs in less than 10% of patients treated with Nivolumab for lung cancer in clinical trials. This is due to autoimmune colitis. The timing of onset of colitis tends to be after 6-8 weeks of treatment. Diarrhea at this level – 6x/day is Grade 2 diarrhea. The recommended treatment would be oral steroids however if symptoms failed to settle/improve within 3 days or worsened IV steroids would be indicated.

Authors

Dr Riyaz Shah
Consultant Medical Oncology
Kent Oncology Centre
Maidstone Hospital
Barming, Kent, ME16 9QQ
Riyaz.Shah@nhs.net

Dr Justin Waters
Consultant Medical Oncology
Kent Oncology Centre
Maidstone Hospital
Barming, Kent, ME16 9QQ
Justin.Waters@nhs.net

Dr Ciara O'Hanlon Brown
SpR Medical Oncology
Kent Oncology Centre
Maidstone Hospital
Barming, Kent, ME16 9QQ

Corresponding Author

Dr Ciara O'Hanlon Brown
Ciara.O'HanlonBrown@nhs.net

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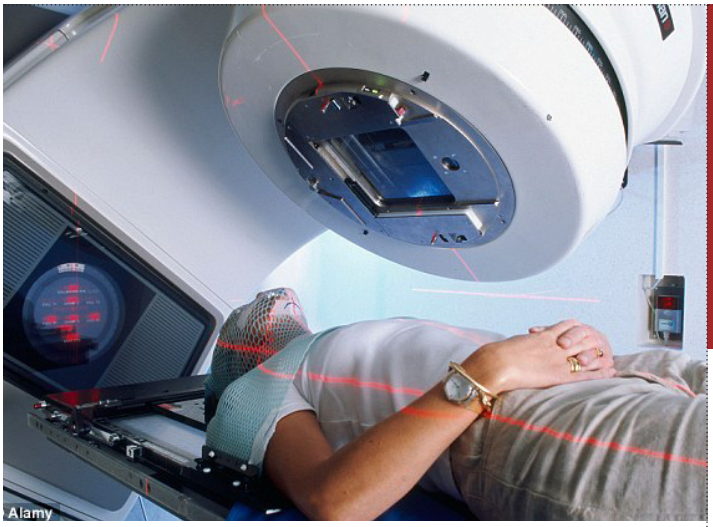
SHORTNESS OF BREATH FOLLOWING RADIOTHERAPY FOR LUNG CANCER

A Garcia, S Walters



Abstract

Nearly two thirds of patients with cancer will undergo radiation treatment and with ever increasing advances in treatment and survival, understanding of the complications of radiotherapy is imperative across the specialities.

Radiation pneumonitis is a common and anticipatable consequence of radiotherapy at "radical" doses resulting from damage to pneumocytes and in some cases inducing an immune mediated response throughout the lungs. In 1.9% of cases of patients being treated with combined modality chemotherapy and radiotherapy, this can be fatal. Many patients will in addition suffer from superimposed infection or complications from their chemotherapy or radiotherapy.

The article focuses around Patient A and discusses the difficult clinical presentation and interpretation of investigations associated with this condition. In addition this article aims to promote early recognition of radiation pneumonitis and help identify which patients are particularly at risk.

Case History

Our case focuses on Patient A, a 68 year old gentleman that presented to his GP with a persistent cough but was otherwise in good health except for a previous heavy smoking history of 40 pack years. A chest x-ray was arranged which identified an abnormality in the right lower lobe and subsequent CT chest/abdomen/pelvis scan confirmed a mass localised to right lower lobe with mediastinal lymph node enlargement.

Shortness Of Breath Following Radiotherapy For Lung Cancer
Patient Management

Lymph node sampling was performed by endobronchial ultrasound (EBUS) which confirmed the diagnosis of squamous cell lung cancer, stage T3 N2 M0 (TNM staging or stage 3) (1).

A number of factors are pertinent to the assessment of patients with a diagnosis of lung cancer namely the extent of disease, patient co-morbidities and baseline lung function which in Patient A case was an FEV1 of 3.3L (103%) and an FEV1/FVC ratio of 70. A radical (meaning potentially curative) course of combined chemotherapy and radiotherapy treatment was agreed upon following MDT review and patient counseling.

Concurrent chemotherapy-radiotherapy means a single or twice daily radiotherapy treatment to the lung mass and in this case the involved mediastinal lymph nodes over 6 weeks, (66 Gy in 33 fractions over 26 days), with two cycles of chemotherapy during the first and final weeks. Standard chemotherapy for this regime would be combination therapy with Etoposide 50mgs/m2 prior to radiotherapy on day 1-5, D29-33 and Cisplatin 50mg/m2 D1-8 and D29-36. Different cancer centres may have slightly different protocols however the overarching principals remain the same.

Overall Patient A tolerated the treatment well with few side effects. He was reviewed 2 months after treatment completion in the outpatients complaining of slowly progressive shortness of breath. There was no history of systemic upset or symptoms compatible with embolism and his chest x-ray (Figure A) showed extensive changes in the right lower zone.

Over the following week however he deteriorated with worsening shortness of breath and he was admitted to hospital where investigations ruled out infection including atypical infections and pulmonary embolism. A CT thorax (figure B), confirmed a diagnosis of extensive radiation pneumonitis.

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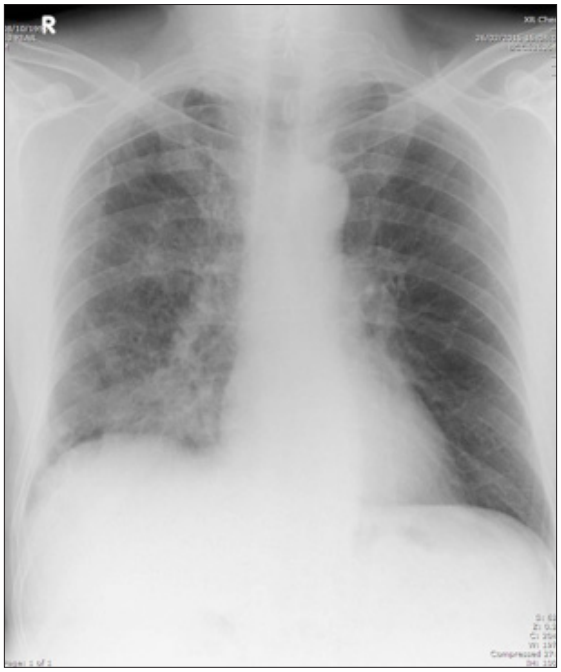

Figure A: Chest radiography showing extensive changes in right base and midzone.

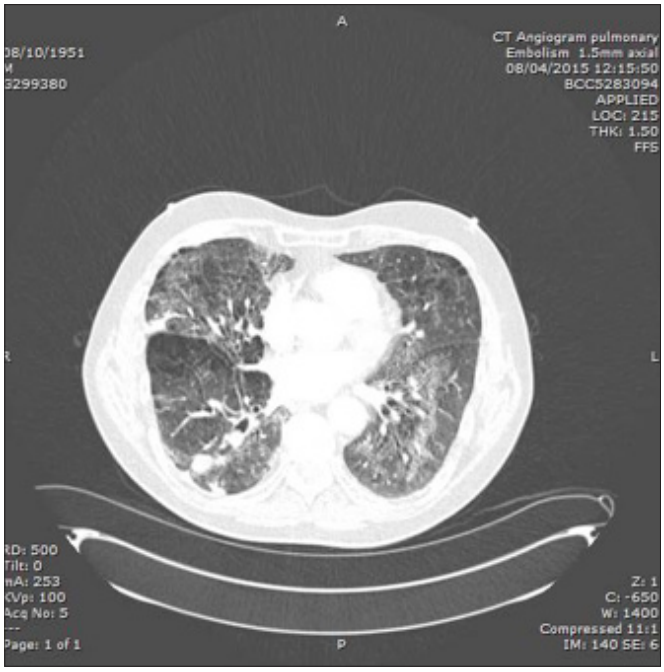

Figure B: Patchy interstitial shadowing bilaterally, particularly in the right lung extending beyond previous radiotherapy treatment field.

Patchy interstitial shadowing bilaterally, particularly in the right lung extending beyond previous radiotherapy treatment field.

Concurrent chemotherapy/radiotherapy

Concurrent chemotherapy and radiotherapy is an aggressive treatment offered to patients with potentially curative disease, provided they are fit enough as defined by the WHO performance status (2) (appendix 1). Chemotherapy sensitises cancer cells to the kill effects of radiotherapy, however the combination can be toxic. Toxicities are anticipatable and radiographers, physicists and clinicians are involved in the planning of treatment to try and limit problems.

The risk of Radiation pneumonitis is a serious consideration in radiotherapy planning. Many patients following completion of their treatment will suffer to a certain degree but is usually mild. Life threatening radiation pneumonitis is rare but represents one of a number of significant treatment toxicities that it is paramount to assess for with any patient receiving chemotherapy-radiotherapy.

Other sequels to assess for include radiation induced oesophagitis, neutropenic sepsis, cisplatin or dehydration related renal failure and electrolyte disturbances (hypocalcaemia, hypomagnesia). In general patients must be closely monitored during therapy with weekly medical review and blood test and early outpatient review on treatment completion. In extreme cases radiation pneumonitis can be a life threatening complication of treatment with a meta-analysis in 2013 showing fatal pneumonitis in 1.9% of patients treated concurrently (3).

What is radiation pneumonitis?

Radiation pneumonitis is caused by pulmonary interstitial inflammation from epithelial damage and subsequent cytokine release. It is characterised by loss of type 1 and 2 pneumocytes and therefore surfactant with increased capillary permeability leading to interstitial and alveolar oedema. In addition it is possible to develop an immunological mediated pneumonitis outside of the radiation field i.e. in the non irradiated lung.

The risk factors for development of radiation pneumonitis broadly fall into 2 categories, those related to the patient and those related to the treatment profile.

Patients over the aged of 65 and with significant co-morbidities are particularly at risk. Middle and lower lung tumours are also associated with increased risk as is previous thoracic irradiation. Smoking status past and present in one review (4). was shown to be protective for the development of radiation pneumonitis however general agreement amongst clinicians is that poor baseline lung function FEV1 less than 1L would preclude a patient from concurrent treatment due to pneumonitis risk and likelihood of debilitating shortness of breath in the long term (3,4).

SHORTNESS OF BREATH FOLLOWING RADIOTHERAPY FOR LUNG CANCER

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Pneumonitis is well recognized with increasing total radiation dose but a sensitive predictor is the V20 value calculated during treatment planning. This refers to the area of normal lung receiving greater than 20 Gy. V20 should be kept to less than 35% to keep the risk of clinically significant pneumonitis to <20% (5).

The severity of radiation pneumonitis is graded according to the following (6):

Toxicity	Grade 0	Grade 1	Grade 2	Grade3	Grade 4	Grade5
Pneumonitis/ pulmonary infiltrates	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated Life-threatening respiratory compromise	Urgent intervention indicated (e.g., tracheotomy or intubation)	Death

Clinical presentation

Cough is a predominant feature along with fever and chest pain. The timing of radiation pneumonitis can occur from the second week of treatment up until 6 months following completion (7).

Examination

Patient examination may range from normal to a patient in extremis (rarely). Clinically there may be crackles, pleural rub, cyanosis or evidence of pleural effusion.

Investigations

Initial investigatory tests and history should focus on excluding obvious alternative causes for shortness of breath namely infection, pulmonary embolism and unfortunately for some patients, disease progression during their treatment.

Baseline investigations should include:

FBC, U+Es, CRP, LFTs- Bloods may be normal or show raised CRP and lymphocytes.

Chest X-ray - features are usually non specific showing mostly atelectasis, consolidation and pleural effusion commonly. A normal film does not exclude the diagnosis.

Computer tomography - this is the investigation of choice. Features include consolidation, ground glass opacities, tree in bud changes and pleural effusions. It is important to remember that changes may extend beyond the radiation field including to the contra-lateral lung.

Specialised tests

Diagnosis is based on clinical features and typical CT findings. CTPA can be necessary to exclude venous thrombotic disease, echocardiogram to assess cardiac function and presence of pericardial effusion. Lymphangitis is an important differential when reviewing findings.

Treatment

Treatment is largely supportive although steroids have some benefit, either Prednisolone 50-60mg/day or dexamethasone 8-16mg/day with gastric cover is recommended. Steroids at these doses must be weaned cautiously to avoid rebound pneumonitis as well as issues related to adrenal suppression. Inhaled steroids are commonly prescribed with reasonable logic however there are no clinical trials to support their use (6). Most patients can be managed as an out-patient, but for those requiring admission, senior oncology advice should be sought early.

Progress

Patient A was discharge home following a period of steroid treatment and monitoring although a month later he presented to A+E unwell with productive cough and offensive sputum. A further CT scan was performed (figure 3), this showed stable disease with regard to his cancer but did show significant consolidation and he was admitted for treatment of what was ultimately diagnosed to be a lung abscess. He was treated with a course of intravenous antibiotics and since discharge has made a significant recovery and is at present under regular surveillance for his cancer.

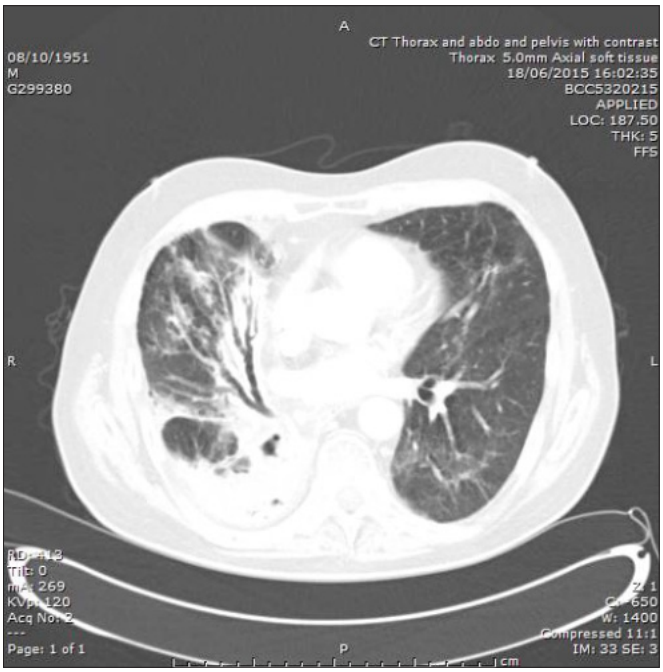

Figure 3

SHORTNESS OF BREATH FOLLOWING RADIOTHERAPY FOR LUNG CANCER

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CT showing progressive extensive right lung consolidation with clinical signs of infection

Discussion

Lung cancer is an increasingly common diagnosis with improving survival rates (Appendix 22); however it can still be viewed unfavourably by the public and some health care professionals. Patients with localised disease, provided they are of good performance status will be offered radical/ potentially curative treatment.

Radiation pneumonitis is easily missed, clinical suspicion should be high in any patient on radiotherapy treatment or within 6 months of completion. Treatment is supportive and with the addition of steroids. In any patient whom continues to deteriorate, diagnosis can be complex. Secondary infections are common however most patients can be managed on an outpatient basis. Any patient unwell enough to warrant hospital admission should be discussed with a consultant oncologist with regard to escalation of care.

Appendix 1

World Health Organisation Performance Status scale

0 - Fully active, more or less as you were before your illness

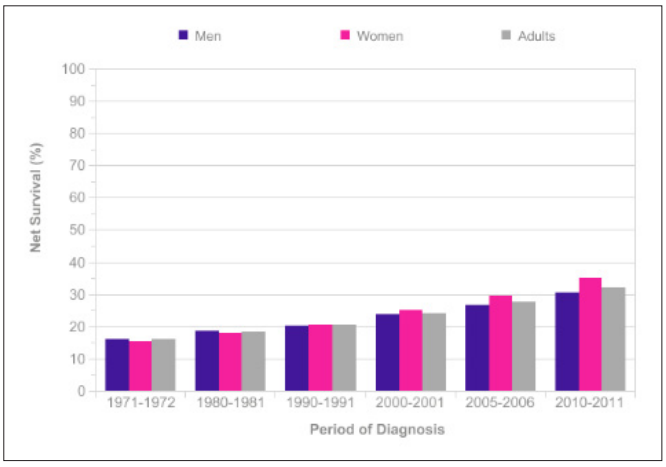
1 - You can't carry out heavy physical work, but can do anything else

2 - You are up and about more than half the day but unable to work

3 - You are in bed or chair for more than half the day. Assistance required for self care

4 - You are in bed or a chair all the time and need complete care

Appendix 2



Age standardized survival at one year from lung cancer, England and Wales.

MCQ

1. Which of the following is the most appropriate therapy to start in a patient with suspected acute radiation pneumonitis?

a. Inhaled Salbutamol - one to two puffs four times daily

b. Oral Prednisolone 30mg once daily with PPI cover

c. Humidified oxygen therapy

d. Inhaled budesonide- two puffs twice daily

e. Oral dexamethasone 8mg twice daily with PPI cover

2. 9 months following completion of radiotherapy a patient describes progressive shortness of breath over the preceding 3 months.

Clinic spirometry shows a reduced FEV1 and FVC compared with pre-treatment however with a higher FEV1/FVC ratio. What is the most appropriate way to investigate?

a. Commence patient on oral dexamethasone 8mg BD and request CT chest

b. Request formal pulmonary function testing including DLCO and CT chest

c. Refer patient for programme of breathing physiotherapy

d. Request CTPA

e. Trans thoracic echo and cardiology referral

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3. Concurrent chemotherapy radiotherapy is the treatment of choice in which of the following cases?

a. Patient with stage 1 adenocarcinoma of the left lower lobe. Performance status 1 , pulmonary function tests (PFTs) show FEV1 of 1.8L

b. Patient with stage 4 adenocarcinoma of the left lower lobe. Performance status 0, PFTs show FEV1 of 1.8L

c. Patient with adenocarcinoma of the left lung approximately 2cm isolated thoracic disease, with solitary liver metastases. Performance status 1, PFTs show FEV1 of 1.8L.

d. Patient with squamous cell lung cancer. Performance status 1, PFTs show FEV1 of 0.8L

e. Patient with squamous cell lung cancer in the periphery of the contralateral lung, T2 (or 4cm), 2 years after radical treatment of a left lung cancer with concurrent chemo-radiotherapy. Performance status 1.

4. Which of the following is not a feature of acute radiation pneumonitis?

a. Pleuritic chest pain

b. Fever

c. Haemoptysis

d. Pleural effusion

e. Productive cough

5. What is the investigation of choice to diagnose acute radiation pneumonitis?

a. Chest X-ray

b. CTPA

c. Trans thoracic echo

d. CT chest

e. All of the above

Answers

1. Answer = e

Although the other options all seem reasonable there is little to no evidence that inhaled medications including inhaled steroids have any benefit. Prednisolone is recognised treatment but at 50-60mg/day.

Dexamethasone has been shown to be helpful. 16mg IV can be given stat but should then be changed to divided doses i.e. 8mg BD.

2. Answer = b

Pulmonary fibrosis should be considered 9 months after treatment and should be referred to respiratory physicians following baseline investigations. CT will also allow evaluation for cancer re-staging. Pulmonary function tests will show a restrictive pattern (normal or increase FEV1/FVC ratio) with reduced lung volume and transfer factor.

3. Answer = c

Patients with early Non small cell lung cancer should be managed with surgery if fit enough for general anaesthetic. Advanced stage 4 cancer treatment aims are palliative and the toxicity associated with combined chemotherapy radiotherapy is too high. In lung cancer unfortunately even in cases of low burden/volume of disease, visceral metastatic disease is not considered curable.

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A minimum of 1L FEV1on PFTs is required otherwise the patient maybe debilitated by shortness of breath post treatment. Following a previous radical radiotherapy dose the patient with recurrent disease would be unlikely to tolerate repeat therapy. These patients should be considered for newer techniques such as stereotactic ablative radiotherapy (SABR)

4. Answer = C

All of the above are features except haemoptysis. This suggests an infective cause or pulmonary embolism. Purulent sputum suggests infection but this is often associated.

5. Answer = d

CT chest is the gold standard however all of the others would be reasonable in the work up of such a patient.

6. Answer = d

CT chest is the gold standard however all of the others would be reasonable in the work up of such a patient.

Authors

Dr Angel Garcia
North Wales Cancer Treatment Centre
Glan Clwyd Hospital
Rhuddlan Road, Bodelwyddan, Rhyl LL18 5UJ
Angel.garcia@wales.nhs.uk

Dr Sarah Walters
North Wales Cancer Treatment Centre
Glan Clwyd Hospital
Rhuddlan Road, Bodelwyddan
Rhyl , LL18 5UJ

Corresponding Author

Dr Sarah Walters
Sarah.walters3@wales.nhs.uk

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SYSTEMIC COMPLICATIONS OF MODERN CANCER TREATMENTS & THEIR CLINICAL MANAGEMENT

BL Onen, AB Hassan, DC Talbot

Abstract

Biological therapies are increasingly used in modern cancer management via activation of the immune system. This approach blocks inhibitory signals that normally prevent the effect of the immune system on cancer. One such example of an immune checkpoint inhibitor is Ipilimumab, which blocks cytotoxic T-lymphocyte antigen 4 (CTLA4). Ipilimumab has been approved for treatment of advanced malignant melanoma and is under investigation for other types of cancer, such as advanced small cell lung cancer.

The impact of these new treatments may change the spectrum of side effects as the use of immunotherapy for the treatment of cancer becomes more widespread. A general understanding of the potential toxicities of immunotherapy is important to ensure patients are investigated and managed promptly. The incidence of autoimmune and inflammatory complications of these treatments is increasing, the most common being colitis (27%), dermatitis (26%), hepatotoxicity (<10%) and endocrinopathies (<10%).

Immune-related endocrinopathies such as hypophysitis are often insidious in presentation, provide a diagnostic challenge due to limited clinician suspicion and can be fatal if left untreated. We present a case of a 57-year old male who was admitted to the acute Oncology service with manifestations of hypophysitis after the fourth dose of Ipilimumab for the licenced indication of metastatic malignant melanoma.

Systemic Complications Of Modern Cancer Treatments & Their Clinical Management
Patient Management

Case history

A 57-year old gentleman presented acutely to the Oncology ward with two-week history of progressive lethargy and muscle weakness starting a day after the fourth dose of Ipilimumab. He had no headache, visual disturbance, behavioural change, weight loss or other systemic signs of note. He had been diagnosed with metastatic melanoma of the left inferior turbinate eight years earlier.

Initial management involved tumour resection followed by radiotherapy. Seven years later, he had local recurrence, requiring further resection. Computed tomography (CT) scans of the abdomen performed five months before this re-admission showed a single liver metastasis. Genomic analysis of his tumour showed BRAF and c-KIT gene wild type. He was commenced on 3mg/kg of Ipilimumab q21 (administered every 3 weeks) for a planned four doses.

He had a history of pulmonary embolism related to a heterozygous mutation for inherited thrombophilia, for which he was taking Rivaroxaban. There was no known history of allergies. He lived with his wife and had normal activities of daily living with a performance status score of one (Eastern Cooperative Oncology Group performance scale).

On admission, temperature was 37 degrees Celsius, blood pressure 110/82 mmHg, pulse 80 beats per minute and regular, respiratory rate of 14 beats per minute and oxygen saturations of 97 percent on ambient air. Physical examination revealed him to be weak and lethargic. Cardiovascular, respiratory, abdominal and central nervous system examination were clinically normal.

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Peripheral blood indices, serum urea, electrolytes and creatinine levels were within the normal range. Low levels of serum cortisol and thyroid stimulating hormone prompted further assessment of pituitary function (Table 1). Hypocortisolism, inadequate cortisol response to synacthen stimulation test, low thyroid stimulating hormone and testosterone level were consistent with the diagnosis of hypophysitis.

He was referred to the endocrinology team and commenced on oral Hydrocortisone with proton pump inhibitor prophylaxis. The initial Hydrocortisone schedule commenced was 20 mg in the morning and 10 mg in the afternoon and evening for 3 days; followed by half the doses subsequently. Other treatments included Testogel and Levo-thyroxine 50 micrograms daily. He had a satisfactory clinical response and was discharged two days after admission.

On review in the Oncology clinic two weeks later, improvements in his clinical and biochemical profiles were confirmed (Table 1). Severe claustrophobia deterred magnetic resonance imaging (MRI) of the pituitary gland. Restaging CT scan after four doses of Ipilimumab showed disease progression. He was palliatively managed with community palliative care support.

Discussion

Oncology patients on chemotherapy often present to acute medical services with conditions related to disease progression and common side-effects to drugs. In the last decade, many more biological agents such as therapeutic antibodies and small molecule inhibitors have been utilised in cancer treatment; thus widening the spectrum of presentations relating to adverse side effects to cancer treatments.

Ipilimumab is an example of an immune checkpoint inhibitor that blocks an immune target (cytotoxic T-lymphocyte antigen 4, CTLA4) and has expanded indications in cancer. It is approved for treatment of advanced melanoma and is under investigation for other types of advanced cancer, for example, small cell lung cancer.

The most common side effects are colitis (27%), dermatitis (26%), hepatotoxicity (<10%) and endocrinopathies (<10%) (1) (see table 2) (2). Rarer auto-immune related toxicities (<1%) include neurological (Guillain-Barré syndrome), ocular and renal insufficiency (1). Though rare, endocrinopathies such as hypophysitis often have an insidious presentation, providing a diagnostic challenge to clinicians with low indices of suspicion of this adverse effect. Left untreated, it can be fatal.

Summary Of Common Immune-Related Endocrinopathies (Table 2)

Endocrinopathy	Symptoms	Treatment
Hypothyroidism	Fatigue, weight gain	Thyroid hormone replacement
Hyperthyroidism	Fatigue, weight loss	Carbimazole, corticosteroids
Adrenal insufficiency	Dehydration, hypotension, electrolyte imbalances (hyperkalaemia, hyponatremia)	Corticosteroids
Hypophysitis	Fatigue, nausea, change in mental status	Corticosteroids, hormone replacement as required
Diabetes	Polydipsia, polyuria, lethargy, weight loss	Insulin

Autoimmune hypophysitis secondary to Ipilimumab therapy was the most probable diagnosis in the case presented. Hypophysitis is a rare inflammatory condition of the pituitary gland. Pathogenesis is unknown, but likely to be autoimmune (3). With the advent of immunomodulating agents, hypophysitis appears to be increasing in frequency (3) (4). Symptoms are often vague and can include fatigue, headache, altered mental status or symptoms of hypothyroidism (5).

Diagnosis is made by establishing low levels of hormones produced in the pituitary; adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. Initial low random cortisol/TSH often prompts further investigation. However, the nonspecific nature of the presentation should encourage consideration/exclusion of other differential diagnoses.

Primary Adrenal Insufficiency & Primary Hypothyroidism

The symptoms presented in the case can mimic primary adrenal insufficiency or primary hypothyroidism. Blood markers can assist with differentiating these diagnoses from hypophysitis. Primary adrenal insufficiency presents with low cortisol, inadequate serum cortisol response to synacthen stimulation test and high ACTH. Primary hypothyroidism is a combination of low T3/4 and high TSH.

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Progression Of Underlying Metastatic Disease Or New Brain Metastases

Fatigue could be attributed to progression of underlying metastatic disease or new brain metastases. Restaging CT is useful for assessing disease response/progression to treatment. Gold standard for differentiating between hypophysitis and pituitary metastasis is a pituitary biopsy (5).

However, given the invasive nature of this procedure, MRI scans of the pituitary gland are preferred. This patient could not undergo this investigation due to claustrophobia. Findings of enhancement or a swollen pituitary gland on MRI would be in keeping with hypophysitis. Clinical and biochemical improvement with steroid and hormone therapy would also be in keeping with the diagnosis.

Other Autoimmune Conditions

Ipilimumab was the likely causative agent of hypophysitis in this case, however, other autoimmune conditions that can predispose hypophysitis should be considered (25% of cases) (6). Immune-related adverse events with Ipilimumab commonly occur between 4.3-7.7 weeks following initiation of treatment and usually begin between the third and fourth dose (6). Occasionally they can present several months after treatment has been completed.

Management

When hypophysitis is diagnosed, Ipilimumab should be withheld in symptomatic patients. Corticosteroids are administered, usually at a dose of 1-3mg/kg/day of prednisolone or equivalent and subsequent appropriate hormone treatment. If there are signs of adrenal crisis such as hypotension/shock, intravenous corticosteroids should be given immediately.

Endocrinopathies may resolve, but some patients are known to require long term treatment. Once managed, endocrinopathies are not a contraindication for further Ipilimumab treatment; however, cautious monitoring of endocrine function is important prior to any further doses (6).

Conclusion

The case highlights the importance of identifying complications of immunotherapy and emphasises that early initiation of therapy can improve outcome. As the use of immunotherapy for the treatment of cancer becomes more widespread, the incidence of autoimmune and inflammatory complications of these treatments will increase. Patients experiencing side effects of these treatments may present with diverse symptoms. Therefore a general understanding of the potential toxicities of immunotherapy is important to ensure patients are diagnosed and treated promptly.

Questions MCQ

1. What are the symptoms of hypophysitis?

A: Lethargy

B: Weight gain

C: Change in mental status

D: Headache

E: All of the above

2. A 50 year old man day 3 post third dose of Ipilimumab presents with a one week history of lethargy, weight gain and poor appetite. Bloods results showed TSH 0.15 mU/L (0.30-4.20), T3 3.0 pmol/L (2.6-5.7), morning testosterone 2.7 nmol/L (8.4-22.7), 9am cortisol 30 nmol/L (>400), serum glucose 4.7 mmol/L. Given the likely diagnosis, what is the first line of treatment?

A: Levothyroxine

B: Corticosteroids

C: Testosterone

D: Insulin

E: Carbimazole

3. If there is biochemical and clinical resolution of hypophysitis, can Ipilimumab be re-started?

A: Patient should not have further biological therapy

B: Ipilimumab can be continued without need for further monitoring of endocrine function

C: Ipilimumab should be switched to Dacarbazine

D: Ipilimumab can be continued with close monitoring of endocrine function

E: Patient should be off corticosteroids before restarting Ipilimumab

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4. A 60 year old man with metastatic melanoma, presented with collapse. He was post a second dose of Ipilimumab that was administered 14 days ago*. His GP had started antibiotics for a chest infection two days prior.

He mentioned five month history of progressive lethargy, constipation and loss of libido. On examination he had sparse hair, and neurological examination revealed diplopia on left lateral gaze. Blood pressure was 80/40mmHg. What is the most likely diagnosis?

** Note that Ipilimumab is given every three weeks for up to four treatments.*

Investigations are shown with normal ranges in brackets:

Test	Result (range)
Hb	94 g/L (130-170)
WCC	7.81x10^9/L (4.0-11.0)
Plt	316x10^9/L (150-400)
MCV	80fl (83-105)
Na	130mmol/l (135-145)
K	4.0mmol/l (3.5-5)
Urea	8mmol/l (3.0-9.2)
Creat	90mmol/l (64-104)
Glucose	5mmol/l
TSH	0.3mu/l (0.3-4.2)
CXR	Normal
12 lead ECG	Sinus bradycardia 60 beats/min
MRI head	Enhanced pituitary gland

A: Addison's disease

B: Primary hypothyroidism

C: Pituitary tumour

D: Diabetes

E: Autoimmune hypophysitis

5. A 50-year old woman with rheumatoid arthritis was recently diagnosed with metastatic melanoma and commenced on Ipilimumab. What complication will she be more prone to as a result of Ipilimumab?

A: Nail discolouration

B: Osteoporosis

C: Tinnitus

D: Double vision

E: Lipodystrophy

Answers

1. E All of the above

Autoimmune hypophysitis can present insidiously with nonspecific symptoms. High index of suspicion is required to make the diagnosis, with treatment resulting in good symptom, radiological and biochemical resolution.

2. B Corticosteroids

The likely diagnosis is hypophysitis secondary to Ipilimumab. Hypocortisolism is life threatening, and steroids should be administered first before other hormone replacement. In the case described, with low T3/T4 levels, additional levothyroxine and testosterone (testogel) should be given after steroids.

Low TSH/cortisol levels sometimes causes confusion and problems differentiating hypophysitis from primary adrenal insufficiency and hypothyroidism. Primary adrenal insufficiency presents with low cortisol, inappropriate cortisol stimulation test and high ACTH. Primary hypothyroidism is a combination of low T3/4 and high TSH.

3. D Ipilimumab can be continued with close monitoring of endocrine function

Although some patients have full resolution of hypophysitis, others require long term corticosteroid and hormone therapy. Once managed, endocrinopathies are not a contraindication for further Ipilimumab treatment; however, cautious monitoring of endocrine function is important prior to any further doses.

Clinicians can decide on clinical grounds whether Ipilimumab should be discontinued. Dacarbazine is an alkylating agent that hinders cell growth by inhibition of DNA synthesis. It has fewer side effects to Ipilimumab, but is less effective.

SYSTEMIC COMPLICATIONS OF MODERN CANCER TREATMENTS & THEIR CLINICAL MANAGEMENT

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4. C Pituitary tumour

Symptoms of fatigue and low libido should cause suspicion for hypopituitarism. Gonadotrophin deficiency also causes loss of libido. Hypotension and low sodium likely represent cortisol depletion secondary to low ACTH reserve. Normal potassium makes Addison's disease (primary hypoadrenalism) less likely. Low TSH suggests secondary hyperthyroidism, likely due to pituitary disorder. Extra ocular muscle dysfunction suggests pituitary tumour due to pressure on the cavernous sinus. The most likely diagnosis is pituitary tumour, secondary to metastatic disease.

5. D Double vision

Ipilimumab works on the immune system by blocking inhibitory signals that normally prevent the effect of the immune system on cancer. This commonly causes auto-immune related adverse side effects such as dermatitis, colitis, hepatotoxicity and endocrinopathies. Diplopia caused by autoimmune thyroiditis is the most likely answer here.

Test	Pre treatment	14 days Post treatment
ACTH (0-46)	24.9 ng/L	-
9 am Cortisol (>400)	<22 nmol/L	210 nmol/L (random)
30 minutes post synacthen	62 nmol/L	-
60 minutes post synacthen	86 nmol/L	-
TSH (* 0.30-4.20)	0.2 mU/L	1.11 mU/L
Free thyroxine (* 9.0-19.0)	7.5 pmol/L	-
FT3 (2.6-5.7)	3.8 pmol/L	-
Prolactin (70-410)	<12 mU/L	16 mU/L
LH (0.6-13.0)	1.4 IU/L	3.0 IU/L
FSH (1.0-12.0)	3.4 IU/L	3.5 IU/L
Testosterone (8.4-22.7)	3.2 nmol/L	19.5 nmol/L
Glucose	4.8 mmol/L	5.7 mmol/L

Table: Blood results at acute presentation and after treatment for 14 days (Table 1)

Authors

Dr Barbara Lachana Onen
CT3, Department of Oncology
Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE

Professor Andrew Bassim Hassan
Professor of Medical Oncology and Consultant in Medical Oncology
Department of Oncology Churchill Hospital, Oxford University Hospitals
Old Road, Headington, Oxford, OX3 7LE
bass.hassan@path.ox.ac.uk

Professor Denis Charles Talbot
Professor of Cancer Medicine and Consultant in Medical Oncology
Department of Oncology Churchill hospital
Old Road, Headington, Oxford, OX3 7LE
denis.talbot@oncology.ox.ac.uk

Corresponding Author

Dr Barbara Lachana Onen
barbara_lachana@hotmail.com

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THE EVOLUTION OF NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT

J Longley, B Eccles, A Drury, T Geldart

The Evolution of Non-Small Cell Lung Cancer (NSCLC) Treatment
Patient Management

Abstract

The management of NSCLC is entering a new era in the form of treatment with immunotherapy and personalised targeted therapies. These new drugs are associated with a different toxicity profile compared to traditional chemotherapy. The following case will illustrate the anti-cancer properties and side effects associated with the new immunotherapy drug Nivolumab, and how this differs from the historic standard of care with cytotoxic chemotherapy.

Case History

A 49 year old gentleman was referred to our Oncology Department with Stage IV non-small cell (adenocarcinoma) of the lung. Standard somatic genetic testing of his tumour biopsy for epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations revealed no targetable mutations and as such commenced treatment with Cisplatin and Pemetrexed chemotherapy. He had no other past medical history and was independent with a performance status of 0.

Following his first cycle of chemotherapy he unfortunately suffered a myocardial infarction and a thrombotic stroke that impacted his speech and motor function. After a full neurological recovery he decided to resume chemotherapy with Carboplatin instead of Cisplatin which is less pro-thrombotic. An end of treatment CT scan after four cycles showed disease response and Radiotherapy was used to consolidate this substantial response to chemotherapy.

He then commenced maintenance Pemetrexed chemotherapy until disease progression 9 months later. During this period he developed a solitary posterior fossa brain metastasis which was surgically resected without complication and he remains relapse free from a central nervous system (CNS) perspective.

At the point of disease progression, with an eye to future treatment options, he was enrolled into the Stratified Medicine Programme (SMP2), a clinical trial evaluating large scale molecular testing of patients with NSCLC using next generation sequencing. Tissue retrieved from his brain metastasis was analysed for 28 candidate genes as part of the study and a number of tumour specific genetic abnormalities were demonstrated including the presence of MET gene amplification.

The SMP2 trial results feed into the UK Matrix trial, a phase II, multi arm, genetic marker directed trial in advanced lung cancer. The presence of MET amplification will mean that the patient will in the future be eligible for an experimental treatment arm evaluating Crizotinib (an agent already in use for patients with known ALK translocations) if and when all standard treatment options are exhausted.

Whilst SMP2 testing was being carried out, the patient was switched to treatment with Nivolumab, a monoclonal antibody directed against the programmed death 1 (PD1) receptor. Recent phase III evidence has demonstrated a dramatic improvement in outcome and tolerability for patients treated with this agent in comparison with the long established standard second line chemotherapy treatment Docetaxel (1). A CT scan at baseline and to assess response following three cycles can be seen in Figure 1.

This shows a marked reduction in previously enlarging metastatic abdominal lymphadenopathy. Although treatment was well tolerated with minimal side-effects, treatment related diarrhoea occurred after several cycles of treatment. A tapering course of steroids led to rapid resolution of symptoms and he remains on Nivolumab treatment which continues to prove effective with minimal associated toxicity.

THE EVOLUTION OF NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT

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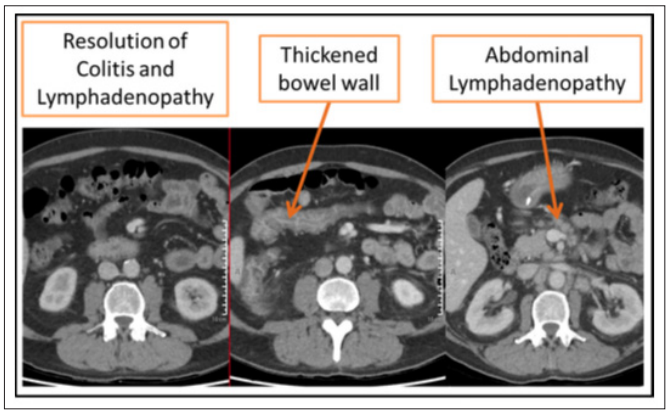

Figure 1: CT Scans showing Lymphadenopathy prior to commencing Nivolumab, Colitis following 3 cycles of Nivolumab given fortnightly and resolution of both in most up to date scan.

Discussion

Cytotoxic therapy

Cisplatin is a platinum based cytotoxic drug which has been effective in the treatment of solid tumours for the past 30 years. Its mechanism of action involves the cross-linking of DNA, leading to tumour DNA damage and activation of cell apoptosis (2). The most common adverse effects of Cisplatin include nausea and vomiting, nephrotoxicity, neuropathy and an increased risk of thromboembolic events (3).

Carboplatin is also a platinum based chemotherapy agent with a similar mechanism of action to Cisplatin but a different side effect profile. Secondary prophylaxis with Enoxaparin was also added and the patient suffered no further thrombotic events during the rest of his treatment.

Immunotherapy

One mechanism by which cancer cells can evade the immune system is by displaying ligands which inhibit T cell activation. Nivolumab is a monoclonal antibody which blocks the Programmed Cell Death (PD1) inhibitory receptor displayed on the T cell surface, preventing it from binding with its ligand (PDL1) on the tumour cell surface (1). Figure 2 shows how Nivolumab acts as checkpoint inhibitor between tumour cells and T cells enabling the cellular immune response to exert its anti-tumour activity.

Many large Phase 3 clinical trials looking at PDL1 inhibitors versus standard of care in different cancer types have shown encouraging results in terms of duration of response and progression free survival (1,4). Median overall survival for patients with NSCLC non-squamous type was 12.2 months in the Nivolumab group versus 9.4 months in the standard of care with Docetaxel group (4).

The toxicity profile associated with immunotherapy is quite different to that seen with cytotoxic chemotherapy and is caused by general immunological activation resulting in effects on the endocrine, dermatological, gastrointestinal and hepatic systems. Common immune mediated side effects include colitis, thyroid disturbance, hypophysitis, dermatitis, hepatitis and pneumonitis (5).

Treatment of significant toxicity requires immunosuppressive therapy with corticosteroids and is usually effective in controlling symptoms as in our patient who was treated with dexamethasone. In severe cases tumour necrosis factor alpha antagonists such as Infliximab may be required to control the overactive immune response (5). Patients with concurrent autoimmune disease provide a difficult challenge, as it is suggested that immunotherapy may exacerbate symptoms. These patients were excluded from clinical trials on this basis and there is currently therefore no clinical evidence to provide guidance for clinicians (1).

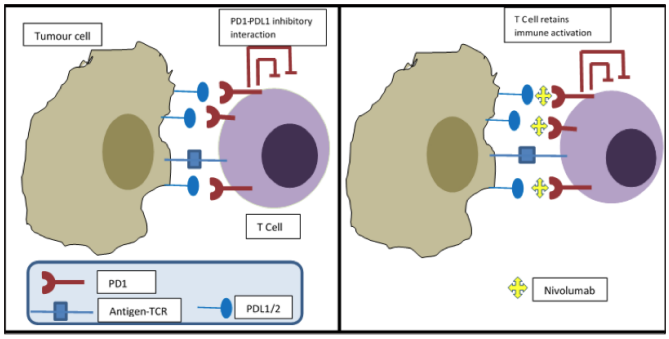

Figure 2: Mechanism of action of Nivolumab.
TCR = T Cell Receptor

Targeted therapy

The discovery of key mutations that drive oncogenesis has led to the development of drugs which are able to target mutations unique to an individual's cancer genome which are key drivers in the neoplastic process. Many genetic abnormalities have been described within the NSCLC genome. Two key abnormalities are now routinely screened for in advanced NSCLC; EGFR mutations and ALK translocations (seen in 10-15% and 1-2% of the UK screened NSCLC adenocarcinoma population respectively).

The presence of either of these genetic abnormalities is associated with marked sensitivity to the orally available EGFR tyrosine kinase inhibitors (e.g. Gefitinib, Erlotinib, Afatinib) or ALK inhibitors (e.g. Crizotinib). These agents are highly active in patients with these driver mutations, are significantly more effective than standard cytotoxic chemotherapy and are associated with a different spectrum of toxicity and overall, a much lower incidence of significant side effects including rash, diarrhoea and fatigue (6).

THE EVOLUTION OF NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT

J Longley, B Eccles, A Drury, T Geldart

Treatment is in the form of oral tablets and outpatient based which is popular with patients. Novel tumour specific genetic abnormalities are now being screened in large scale trials such as SMP2 with actionable abnormalities such as MET amplification in this case being selected for treatment with available targeted drugs where early phase clinical research suggest promising anticancer activity.

Conclusion

Targeted treatments and immunotherapy are now at the forefront of current cancer treatment and research and it is important to understand the different ways in which patients present with symptoms related to their cancer while taking these drugs and their potential side effects.

Future research is likely to concentrate on mechanisms of drug resistance and identification of many more targetable genetic mutations in tumour DNA. With an ageing population and our increasing ability to prolong life with these new cancer treatments, patients will present across all specialities requiring the general clinician to have a basic knowledge of this fascinating field of medicine.

Best of Five Questions with explanation

1) What is the mechanism of action of Cisplatin?

a. Folate anti-metabolite

b. Cross linking of DNA

c. Topoisomerase inhibitor

d. Induction of DNA strand breakage

e. Stabilisation of microtubules

2)Nivolumab blocks the inhibition of which immune cell?

a. Antigen Presenting Cell

b. T cell

c. Tumour Cell

d. B cell

e. All of the above

3)Cisplatin toxicity includes

a. Myelosupression

b. Nephrotoxicity

c. Thrombosis

d. Peripheral neuropathy

e. All of the above

4) Which of the following is not an immune mediated side effect of Nivolumab?

a. Hepatitis

b. Colitis

c. Hypothyroidism

d. Myelosupression

e. Hypophysitis

5)What is the first line treatment of immune mediated colitis?

a. Infliximab

b. Mycophenolate mofetil

c. Corticosteroids

d. Rituximab

e. Azathiaprine

Answers

1. Answer B

Cisplatin causes cross linking of DNA within cells leading to apoptosis. Over time tumour cells adopt mechanisms of resistance including reduced uptake of the drug, upregulation of DNA repair mechanisms and mutations in the p53 tumour suppressor gene vital for apoptosis. This eventually leads to drug failure and disease progression over time.

THE EVOLUTION OF NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT

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2. Answer B

Nivolumab blocks the inhibition of T cells by acting on PDL1. This upregulates the immune system response to cancer cells, leading to T cell infiltration which may initially cause a worsening of symptoms and apparent disease progression on CT before tumour shrinkage.

Radiological criteria for reporting disease progression have been modified in light of this finding and it therefore important to be aware of different patterns of disease behaviour dictated by the type of anti-cancer therapies.

3. Answer E

Cells that are rapidly dividing are most susceptible to Cisplatin; therefore cells in the bone marrow and gut are most commonly affected. Cisplatin is renally excreted and accumulation within renal parenchymal cells can lead to nephrotoxicity and acute renal failure.

4. Answer D

Myelosupression is commonly caused by cytotoxic chemotherapy regimens.

5. Answer C

Corticosteroids are the first line treatment of immune mediated colitis caused by Nivolumab. A dose of 0.5mg-1mg/kg of methylprednisolone is recommended. In more severe cases and in those refractory to steroids, other immunosuppressive may be considered such as Infliximab and Mycophenolate mofetil. A stool sample should be obtained to rule out opportunistic infections such as Clostridium Difficile.

Authors

Dr Jemma Longley
Specialist Registrar in Medical Oncology
Royal Bournemouth Hospital
Castle Lane East, Bournemouth, BH7 7DW
Jemma.longley@rbch.nhs.uk

Dr Bryony Eccles
Consultant in Medical Oncology
Royal Bournemouth Hospital
Castle Lane East, Bournemouth, BH7 7DW
Bryony.eccles@rbch.nhs.uk

Dr Arnie Drury
Consultant Radiologist
Royal Bournemouth Hospital
Castle Lane East, Bournemouth, BH7 7DW
Arnie.drury@rbch.nhs.uk

Dr Tom Geldart
Consultant in Medical Oncology
Royal Bournemouth Hospital
Castle Lane East, Bournemouth, BH7 7DW
Tom.geldarty@rbch.nhs.uk

Correspondence Author

Dr Jemma Longley
Specialist Registrar in Medical Oncology
Royal Bournemouth Hospital
Castle Lane East, Bournemouth, BH7 7DW
Jemma.longley@rbch.nhs.uk

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THE JOURNEY OF A PATIENT TREATED WITH RADICAL CHEMO-RADIOTHERAPY FOR OROPHARYNGEAL CANCER

S Garikipati, K Wallace, BH Foran

Abstract

Chemo-radiotherapy is the treatment of choice for squamous cell cancers of the oropharynx, resulting in excellent oncological outcomes and good functional results for patients. The incidence and significance of HPV (human papilloma virus) associated oropharyngeal cancers is increasing (1).

This case describes a patient presenting with a lump in the tonsillar region who was diagnosed with an advanced squamous cell carcinoma. He was treated with curative intent chemo-radiotherapy. We aim to highlight the typical problems encountered by patients undergoing this treatment and their management. This patient remains well and cancer free 3 years after diagnosis.

Case history

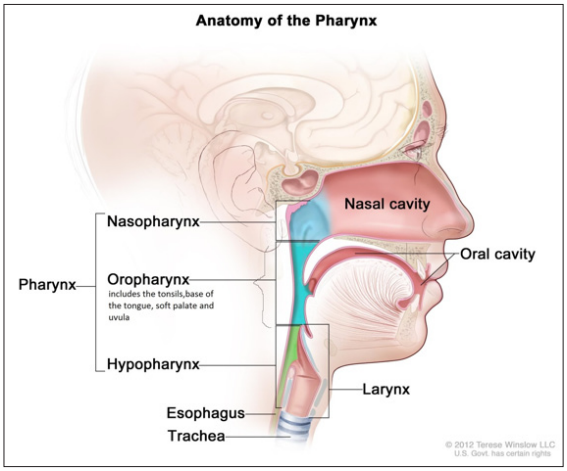
Presentation

A 66 year old gentleman presented with a few weeks history of feeling of a lump in his throat. He denied swallowing difficulties, pain, loss of weight or appetite disturbance. He was initially assessed and investigated in the ENT clinic. His past history included an early thyroid cancer treated 3 years prior with surgery followed by radio-iodine ablation.

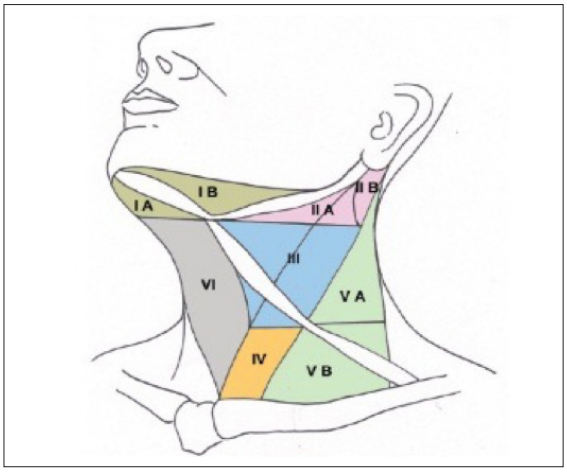
His last thyroglobulin and thyroid function were normal. His regular medication was levothyroxine and nil else, with no known drug allergies. He was a lifelong smoker with a 50 pack year history. His alcohol consumption was 6 units per week. He was a self-employed mechanical engineer. Family history included a sister who died age 64 of lymphoma and a sister treated for bowel cancer.

The Journey Of A Patient Treated With Radical Chemo-Radiotherapy For Oropharyngeal Cancer
Patient Management

Examination revealed an abnormal ulcerated mass in the right tonsillar region along with a 2cm palpable lump in the right upper neck (level 2 region). (See pictures 1 & 2). His tongue movements were normal with no trismus (restriction of mouth opening). His WHO performance status was 0.



Picture 1: Oropharynx.



Picture 2: Neck node levels.

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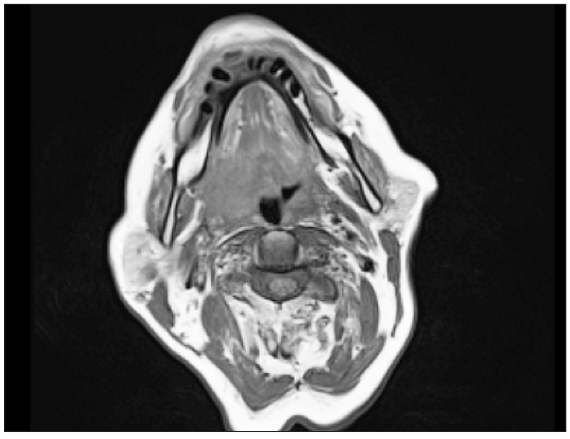
Investigations

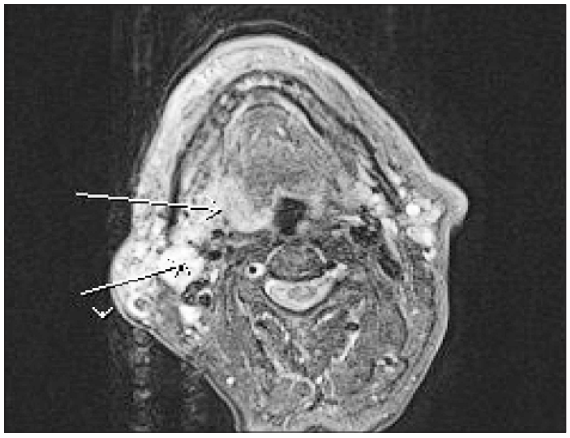
A biopsy of the tonsillar mass confirmed grade 3 (poorly differentiated) squamous cell carcinoma. Immunohistochemistry was strongly positive for p16 (overexpression of which indicates probable association of HPV).

MRI of the head and neck demonstrated a large tonsillar lesion (6cm in maximum diameter) extending to the lateral pharyngeal wall, para-pharyngeal space and tongue base (see pictures 3 & 4). The right level 2 node appeared metastatic while another suspicious lesion was noted on the left side; this was assessed further with ultrasound and biopsy. Staging CT chest was normal. Final TNM stage was T4aN2c M0 ("T" describes the size of the original (primary) tumour, "N" describes the nearby(regional) lymph nodes that are involved and "M" describes distant metastasis.

Picture 3



Picture 4



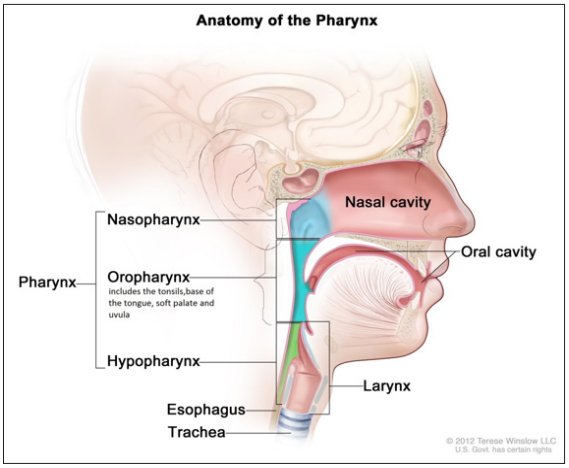
Pictures 3 and 4 are selected MRI slices at the level of the tongue/ tonsil. Upper arrow shows the tumor in the right tonsillar region enhancing with contrast. Lower arrow shows the enlarged right sided level 2 lymph node.

Management

Following discussion in the head and neck multi-disciplinary team meeting, the patient was seen in the oncology clinic and offered curative treatment with chemo-radiotherapy. This involved induction chemotherapy with 'TPF' which is a regime involving 3 cytotoxic drugs, Docetaxel and Cisplatin and 5FU (fluorouracil).

Three cycles were planned to be given over a 5 day admission every 3 weeks. This was to be followed by chemo-radiotherapy delivering 70 Gray in 35 fractions over 7 weeks (Mon-day to Friday) with concurrent cisplatin chemotherapy delivered 3 weekly.

Prior to the induction chemotherapy he required a dental assessment, speech and language as-sessment, nutritional assessment and insertion of PEG (per-cutaneous endoscopic gastrostomy) tube.



Picture 5: PEG (per-cutaneous endoscopic gastrostomy).

During induction chemotherapy

While receiving the first cycle of 5FU infusion, he developed asymptomatic bradycardia with a HR (heart rate) of 45 (see picture 6). The plan was to stop 5 FU infusion if HR fell to <40. His HR did not fall further, but towards the end of the infusion, he became tachycardic (picture 7) with new onset atrial fibrillation which was treated with digoxin. Repeat ECGs did not show ischaemic changes, thyroid function tests were within normal limits as was his troponin T. He was discharged on maintenance digoxin with a diagnosis of probable paroxysmal atrial fibrillation.

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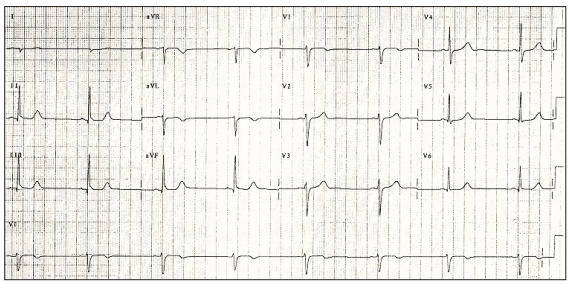
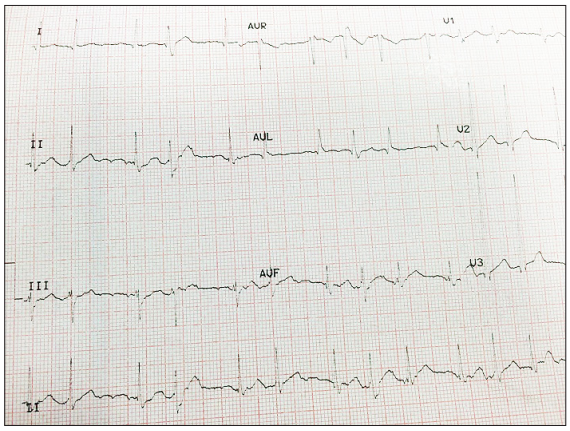


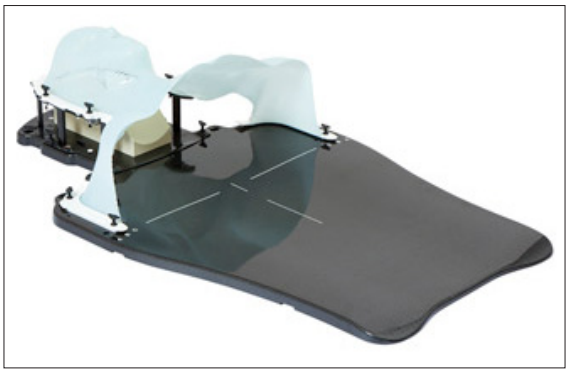
Picture 6a (above): ECG 1- showing sinus bradycardia.



Picture 6b (below): ECG 2-shows irregularly irregular rhythm, absent p waves and a rate of 120/mt—this is tachycardia with atrial fibrillation.

He also had 5FU induced thrombophlebitis treated conservatively. In view of the rate and rhythm problems encountered with the first cycle,5FU was administered at a slower rate over 7 days instead of 4 days during the next two cycles. He completed his planned chemotherapy without any further significant side effects.

He responded well to the induction chemotherapy with resolution of his throat symptoms and the neck node becoming impalpable. He was planned to receive radical chemo-radiotherapy to the oro-pharynx and both sides of the neck following a planning CT scan with a head and neck shell for immobilization (see picture 7).



Picture 7: Head and neck shell for immobilization.

During chemo-radiotherapy

Over the duration of the chemo-radiotherapy he developed progressive mucositis affecting the oral cavity and pharynx. He was treated with regular mouthwashes to prevent infection, alleviate pain and symptoms of dryness in the mouth. Initially, paracetamol was used before escalating to co-codamol and finally to alcohol free oramorph. Swallowing was encouraged throughout the treatment to maintain the muscles of swallowing and enable early rehabilitation.

He used his PEG for supplemental feeds from the 3rd week but after the 5th week of radiotherapy, he was totally PEG dependent for nutritional requirements. He was closely monitored by the dieticians. He lost a considerable amount of weight and needed supplemental feeds through the PEG tube for about 7 months in total during and following completion of his treatment. While continuing with the concurrent chemotherapy, he required 6 units of blood transfused at regular intervals during his chemo-radiotherapy in order to maintain his haemoglobin to over 12g/dl.

Post treatment

His post treatment MRI scan done 3 months following the chemo-radiotherapy did not show any evidence of disease (complete response).(See pictures 8 and 9). His recovery was slow but steady as is expected following this type of treatment. He had a chronic dry mouth (xerostomia) and needed input from speech and language therapists for about 8 months following his treatment, resulting in a good functional recovery. He was last reviewed in November 2015 when he was well without any clinical issues. He underwent an MRI scan in September 2015 which showed no evidence of recurrence (3 years since his diagnosis).

THE JOURNEY OF A PATIENT TREATED WITH RADICAL CHEMO-RADIOTHERAPY FOR OROPHARYNGEAL CANCER

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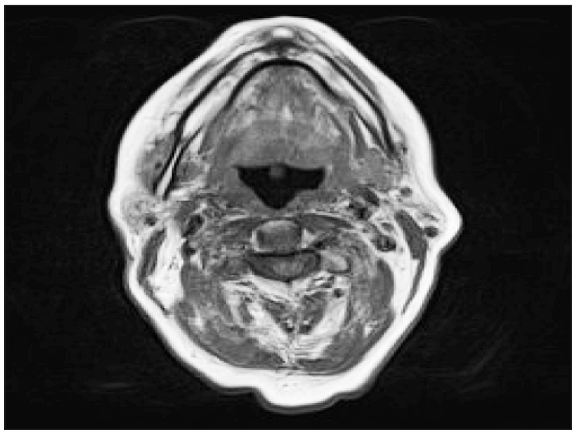
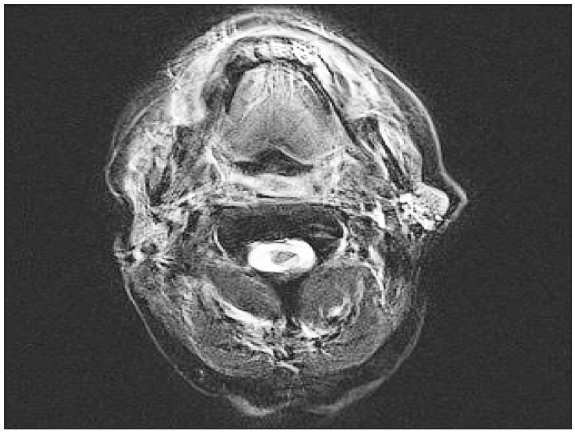
Picture 8



Picture 9



Picture 8 and 9 show the MRI slices at the level of tonsil showing no evidence of tumour(this is the post treatment scan).

Discussion

This patient presented with a locally advanced head and neck cancer with metastatic spread to the regional lymph nodes. This is a common presentation for this kind of malignancy but a high cure rate can still be achieved with chemo-radiotherapy while enabling organ preservation. When combining the two treatment modalities the side effects can be pronounced both in terms of severity and duration.

It is essential to ensure that the curative treatment is not compromised due to poorly controlled side effects which may interrupt the treatment. In this case we know that giving a radical dose of radiotherapy i.e 70 gray in 35 fractions can achieve a cure. In patients with adequate fitness, the addition of chemotherapy enhances the effectiveness of the radiotherapy. (2,3,5,6). Maintaining haemoglobin to at least 12 g/dl to achieve optimal oxygenation is well known to improve overall outcome in radiotherapy for oropharyngeal cancer.(7).

Preparation and planning of treatment requires multidisciplinary involvement and can minimize the impact of treatment side effects. Each chemotherapy drug has a spectrum of likely side effects which can be anticipated and dealt with promptly and appropriately to ensure compliance.

Delays can jeopardise the good outcome which we aim to achieve. 5FU is known to cause coronary artery spasm but abnormalities in the heart rate and rhythm are also possible. Mucositis and dysphagia are inevitable side effects during head & neck radiotherapy and prevent reasonable oral intake hence in our local center the requirement for a prophylactic PEG insertion.

Intensity modulated radiotherapy (IMRT) is a technique whereby the dose delivered to the cancer target is maximized while minimising damage to normal tissues as much as is practical. This helps to decrease long term side effects from radiotherapy for example improving salivary gland function (4). As illustrated in this patient, recovery is a steady, protracted process and close monitoring with continuous multi-disciplinary support achieves the best patient outcomes.

Patients are co-managed by dieticians, speech and language therapists, specialist nurses, radiographers and clinical oncologists to ensure they can complete their treatment on schedule. HPV-positive oropharyngeal cancers represent a distinct disease entity that is causally associated with HPV infection and is also associated with an improved prognosis (1).

This has drawn into question whether we can reduce the intensity of the treatment and still achieve a cure. There are currently clinical trials running aimed to answer this question. (e.g. De-ESCALaTE study).

The above patient will be followed up at regular intervals for a total of 5 years following completion of his radical treatment. Currently he is 3 years post-treatment, well, with no evidence of cancer recurrence.

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MCQs

Q1. Which of these statements is false regarding chemotherapy agents used in oropharyngeal malignancies?

a. Febrile neutropenia occurs in around 80% of the patients receiving TPF chemotherapy.

b. Fluorouracil is given as a continuous infusion of 4 days as part of the TPF regime.

c. In TPF, T stands for docetaxel and P stands for cisplatin.

d. Fluorouracil can cause coronary artery spasm.

e. TPF is a 3 weekly regime.

Q2. Regarding oral intake during chemo-radiotherapy which of the following is true?

a. NG tube (nasogastric) is preferable to PEG tube (Per-cutaneous endoscopic gastrostomy) in head and neck cancer patients undergoing chemo-radiotherapy.

b. Swallowing should be discouraged once it becomes painful.

c. Eating will make the mucositis worse.

d. An obese patient should follow a low calorie diet while undergoing treatment.

e. Duration of PEG usage is entirely dependent upon an individual patient's progress.

Q3. Regarding radiotherapy which of these statements is true?

a. Radiotherapy treatment is skipped on the days when chemotherapy is given.

b. Radiotherapy must be delivered at the same time each day.

c. Radiotherapy cannot cure cancer.

d. Radiotherapy must be given at a minimum of 6 hours between treatments.

e. If a treatment is missed a larger dose is given when they are next due.

Q4. HPV (human papilloma virus) is associated with which of the following squamous cell cancers?

a. Oropharyngeal cancer.

b. Cervical carcinoma.

c. Anal carcinoma.

d. b and c.

e. a, b and c.

Q5. During chemo-radiotherapy for squamous cell head and neck cancer, blood transfusion would be indicated in which of the following patients?

a. Hb 12 g/dL, neutrophils 0.4, platelets-140 admitted with mucositis, decreased oral intake and fatigue in week 5 of CRT(chemo-radiotherapy).

b. Hb 10g/dl, neutrophils 3.5, platelets- 200 seen in radiotherapy clinic with mucositis and no evidence of active bleeding in week 4 of CRT.

c. Hb 12g/dl, neutrophils 0.6, Platelets 80, admitted with febrile neutropenia, mucositis and nutrition problems in week 6 of CRT.

d. Hb 13g/dl, neutrophils 1.5, platelets 120 admitted with with blood stained discharge from mouth in week 6 of CRT.

e. Hb 12g/dl, neutrophils 15.0, platelets 160, CRP 70 admitted with fever, redness and purulent discharge from peg site.

Answers

1. a: *Febrile neutropenia occurs in about 12% of the patients receiving TPF. TPF is a 3 weekly regime. A cycle is based on the time taken for the normal cells to recover therefore at 3 weeks it is usually safe to give another dose of chemotherapy. Docetaxel is also known as Taxotere and is part of a group of drugs known as taxanes and Cisplatin is from the platinum group. 5-Fluorouracil has a very short half-life and is therefore given continuously to maximize the therapeutic benefit.*

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2. e: *It is difficult to predict response to treatment and therefore patients require constant assessment from the multi professional team to ensure management of their symptoms. This enables maximisation of oral intake to maintain their pre-treatment weight and maintain strength and range of movement in the muscles of the oral cavity.*

3. d: *There should be a minimum of 6 hours between treatments. Two treatments can be given on the same day if they have this interval but we would not combine treatments into one session. This is due to the effect on the normal tissue which needs time to recover in the same way as we have determined chemotherapy cycles. Radiotherapy continues even on the days when chemotherapy is delivered. Skipping doses or prolonging treatment can have a detrimental effect on the overall outcome from this treatment. Radiotherapy is an effective treatment which can cure cancer with good functional outcomes for patients.*

4. e: *All three cancers have association with HPV strains 16 and 18. Screening and vaccination have been found effective in cervical squamous carcinomas.*

5. c: *There is significant evidence that radiotherapy works better in oxygenated cells. This can be attained by maintaining haemoglobin level around 12g/dl. Hence a Hb of 10 will warrant blood transfusion despite lack of significant symptoms. In others despite significant symptoms their Hb is stable and other targeted approaches are required.*

Authors

Dr Satya Garikipati
Speciality registrar(ST 6) in clinical oncology
Weston Park Hospital
Sheffield Teaching Hospitals NHS Trust
Whitham Road, Sheffield, S10 2SJ

Dr Katie Wallace
Speciality Registrar (ST 4) in clinical oncology
Weston Park Hospital
Sheffield Teaching Hospitals NHS Trust
Whitham Road, Sheffield, S10 2SJ
katie.wallace2@sth.nhs.uk

Dr B H Foran
Consultant Clinical Oncologist
Weston Park Hospital
Sheffield Teaching Hospital NHS Foundation Trust
Whitham Road, Sheffield, S10 2SJ
Bernadette.Foran@sth.nhs.uk

Correspondence Author

Dr Satya Garikipati
gsvramadevi@gmail.com

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