123 Doc EDUCATION

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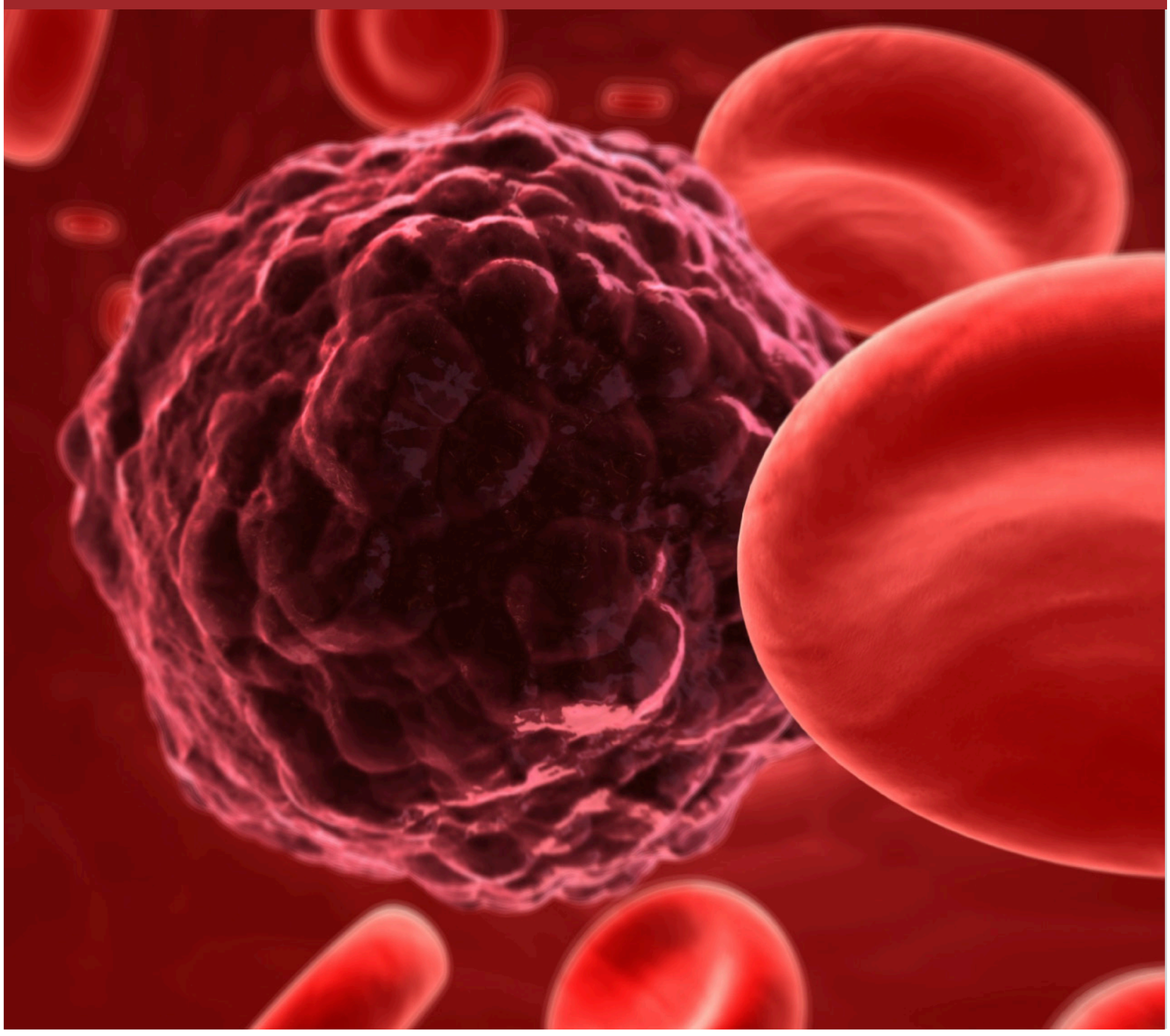

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FOUNDATION YEARS JOURNAL 2010

Volume 4, Issue 4

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Foundation Years Journal is the ONLY journal for Foundation Years doctors and educators, specifically written according to the MMC curriculum. It focuses on one or two medical specialties per month, each issue delivers practical and informative articles tailored to the needs of junior doctors. The Journal closely follows the Foundation Years syllabus to provide the best educational value for junior doctors. In addition to good clinical and acute care articles, assessment questions give junior doctors the chance to gauge their learning. The answers will be published in the next issue, but 123Doc will advance answers to clinical tutor subscribers so they can engage their students in the learning process. Each issue provides comprehensive clinical cases for trainees as well as practical teaching assessments for educators. Readers will benefit from:

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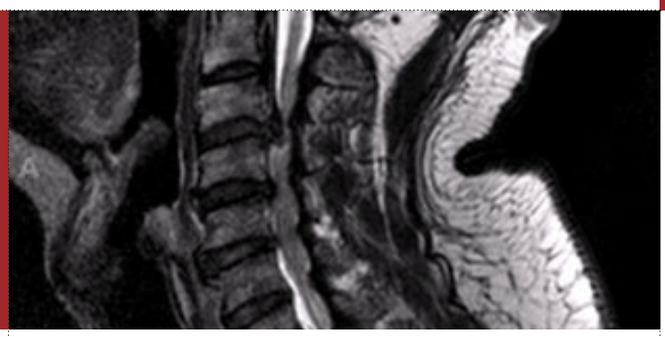
COMMON ONCOLOGICAL EMERGENCIES

Eliyaz Ahamed and Mark Bower



Spinal cord compression.
Patient Management.

Spinal cord compression

Case scenario

You are an SHO in A&E and asked to see a 70-year-old man with known metastatic prostate cancer stage T4NXM1, for which he is receiving anti-androgen therapy. Over the past month he has been complaining of mid-back pain that radiates around his chest when he coughs. This morning he got out of bed and his legs gave way. He also says that over the last week he has noticed increased urinary frequency and now has developed urinary incontinence.

Examination reveals symmetrical weakness of the lower limbs. He had sensory loss below the umbilicus. Knee and ankle jerks are absent with extensor plantar responses. There is pain on palpation of his lower thoracic spine consistent with vertebral collapse secondary to metastatic tumour.

Plain X-ray imaging of the spine shows vertebral collapse of T10. Urgent magnetic resonance imaging of the spinal axis confirms collapse of T10 with extrinsic compression of the thecal sac at this level.

Management

High-dose intravenous corticosteroids should be started on clinical suspicion alone to prevent further evolution of neurological deficit. An urgent neurosurgical opinion should be obtained regarding the potential for surgical decompression if appropriate, especially if there is vertebral instability or the level of the compression has been previously irradiated. Otherwise, the definitive treatment is urgent local radiotherapy.

Further comments

Spinal cord compression from metastatic cancer affects up to 5% of patients and remains an important source of morbidity, even though treatment is effective in 90% of patients if the diagnosis is made early. The most common underlying cancers causing spinal cord compression are breast, lung and prostate cancer, lymphoma and myeloma.

The symptoms at presentation can be vague and often deteriorate before the diagnosis is made. Any cancer patient complaining of back pain, bladder or bowel dysfunction with focal neurology or a sensory level requires urgent investigation. The finding of bilateral upper motor neuron signs should be considered due to spinal cord compression until proven otherwise. Autonomic dysfunction occurs late and carries a poor prognosis. The diagnosis is often made late because more attention is paid to the lack of physical signs rather than the symptoms. Always observe the patients walking if feasible to do so. Remember that the tone is often reduced in the acute setting.

The spinal cord usually ends at L1 level and lesions below this level cause cauda equina syndrome. The thoracic spine is the most common site for spinal cord compression (60%) followed by the lumbosacral spine (30%) and the cervical spine (10%).

Pre-treatment ambulatory function is the main determinant of post-treatment gait function. Patient care requires a multidisciplinary team approach with active rehabilitation following treatment to optimise neurological recovery. Ambulatory function can be preserved in over 80% of patients who are ambulatory at presentation[1, 2, 8].

Superior Vena Cava Obstruction (SVCO)

Case scenario

A 65-year-old woman complains of a persistent but worsening cough. More recently she has noticed that she is more short of breath and that she feels dizzy when she bends forward. Her friends have told her that her voice has deepened and become hoarser over the past few weeks. She feels that she has been putting on weight, as her fingers are swollen and she can no longer wear her rings. She sleeps poorly at night and often wakes up in the morning with “puffy bags” under her eyes. She is a heavy smoker.

On examination, she has a hoarse voice and is short of breath at rest, speaking in broken sentences. She is plethoric with periorbital oedema. Inspection of her chest reveals venous collaterals over her chest wall and upper limb oedema. Her neck veins are engorged with loss of venous pulsation.

A plain chest X-ray shows superior mediastinal widening, which is confirmed on a CT scan that also demonstrates superior vena cava (SVC) compression by tumour and collateral venous drainage via the azygous system, the internal mammary, subscapular and lateral thoracic veins.

COMMON ONCOLOGICAL EMERGENCIES

Eliyaz Ahamed and Mark Bower

Management

The combination of symptoms and signs of SVC are unmistakable. Treatment depends upon the aetiology and severity of the obstruction together with the patient's prognosis, this includes symptom relief as well as treating the underlying cause. SVC with airway compromise is an emergency. Patients should be sat upright and given oxygen therapy. In severe cases high-dose intravenous dexamethasone should be started. When possible a histological diagnosis should be obtained urgently as some tumours are better treated with chemotherapy than radiotherapy. Insertion of an intraluminal stent into the SVC causes rapid relief of symptoms usually within 48 hours. This is the usual emergency treatment while the aetiology of the SVC is established.

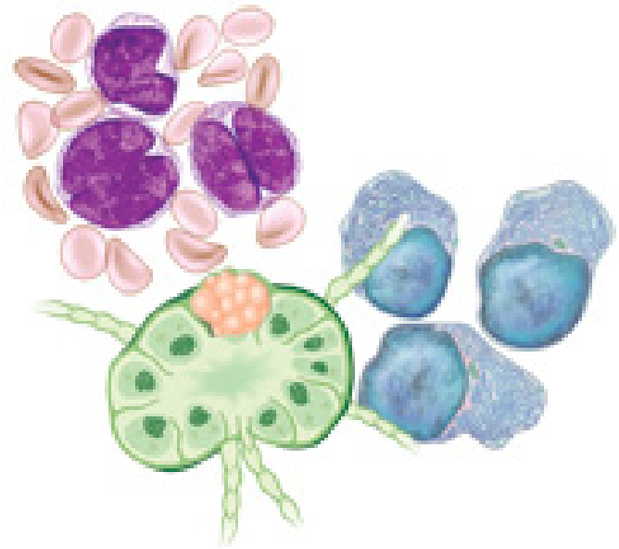
Sputum cytology may establish the diagnosis of small cell lung cancer in many patients, since the majority of patients with SVC have lung cancer (65%) and small cell lung cancer is the main histological type that presents with SVC. Bronchoscopy can yield malignant cells for cytological analysis. In some cases, biopsy of the mediastinal mass may be necessary and this may be achieved either by bronchoscopy, mediastinoscopy or under CT guidance. If a lymph node is palpable or liver metastases are present, biopsy of these may prove to be a faster, less invasive way of establishing the histological diagnosis with lower complication rates. However, in some circumstances, emergency therapy may need to be started before biopsy results are available. For most tumours, mediastinal radiotherapy is the optimal treatment and relieves symptoms in up to 90% of patients within 2 weeks. Although, patients with chemosensitive tumours, such as lymphoma, small cell lung cancer and germ cell tumours gain fast symptomatic relief, within days, from appropriate systemic chemotherapy.

Further comments

The diagnosis of SVC is usually made from the clinical features that arise from obstruction of the venous drainage of the upper body: oedema of the arms and face; distended neck and arm veins; headaches and a dusky skin colouration over the chest, arms and face. Collateral venous circulation may develop over a period of weeks and the direction of blood flow helps to confirm the diagnosis. The most important clinical sign is loss of pulsation in the veins of the neck.

Obstruction of the SVC by mediastinal tumours occurs most frequently with lung cancers, especially small cell lung cancer. The most frequent malignant causes of SVC are: small cell lung cancer; non-small cell lung cancer; lymphoma; germ cell tumours; and breast cancer.

The severity of the symptoms relate to the rate of onset and degree of the obstruction and the development of compensatory collateral venous return. The symptoms may worsen on lying flat or bending, which further limits the obstructed venous return. The outcome of treatment depends on the aetiology of the SVC and response to therapy. Patients with lymphoma, small cell lung cancer and germ cell tumours can have an excellent response to treatment even in the presence of SVC[3, 4].



Tumour Lysis

Case scenario

A 27-year-old man starts his first cycle of CODOX-M (cyclophosphamide, cytarabine, vincristine, doxorubicin and methotrexate) combination chemotherapy for stage 4B Burkitt's lymphoma affecting the bone marrow and cerebrospinal fluid. While on the second day of his chemotherapy, he feels faint and an ECG is performed which shows runs of ventricular tachycardia of up to 4 beats. Urgent biochemistry results are: serum potassium 6.5mmol/L; serum urea 12.8mmol/L; serum creatinine 198mmol/L; serum calcium 1.7mmol/L; phosphate 5.1mg/dl; and serum urate 10mg/dl.

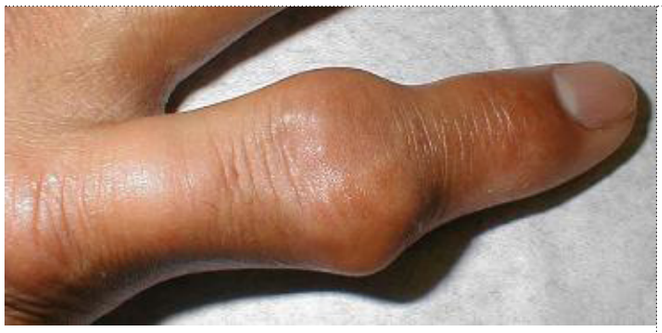
Management

The onset of cardiac arrhythmias during the first cycle of chemotherapy for high grade lymphoma or leukaemia is highly suggestive of tumour lysis syndrome. A brief cardiac history can exclude pre-existing cardiac causes (palpitations, etc.). Important features of metabolic upset include weakness and paralysis (hyperkalaemia), cramps, seizures, spasms and tetany (hypocalcaemia) and urinary symptoms, such as oliguria, flank pain, dysuria and haematuria (acute renal failure). Serum LDH (lactate dehydrogenase) is probably the best test to evaluate treatment response in tumour lysis syndrome.

This patient requires immediate transfer to a high-dependency monitored bed. Tumour lysis results in rapid changes in electrolytes and carries a significant mortality in an otherwise curable tumour type. If the serum potassium is elevated and the ECG shows features of hyperkalaemia, then emergency treatment is required with 10ml intravenous 10% calcium gluconate at once, followed by 50ml intravenous 50% dextrose with 10U short acting insulin over 15–30 minutes with frequent monitoring of BM stix. Metabolic acidosis if present should be treated with 1mmol/kg 8.4% bicarbonate via a central venous line. Assuming normal renal function, hyperhydration by infusion of 0.9% saline, 1 liter/4 hours, with diuresis assisted with furosemide or manitol if urine output is poor should be instituted. Urgent dialysis may be necessary and the emergency dialysis service must be contacted urgently.

COMMON ONCOLOGICAL EMERGENCIES

Eliyaz Ahamed and Mark Bower



Management of hyperuricaemia

Hyperhydration with intravenous fluids can lower the serum urate and reduce the risk of renal failure. In addition, urinary alkalinisation increases urate solubility and hence excretion. This can be achieved by intravenous sodium bicarbonate to achieve a urine pH of 7–7.5. The prophylactic use of allopurinol (a xanthine oxidase inhibitor) should have been started prior to chemotherapy but if not should be administered. A relatively new drug, recombinant urate oxidase (rasburicase) converts uric acid, which is insoluble, into the more soluble allantoin. Clinical trials have shown that rasburicase controls hyperuricaemia faster and more reliably than allopurinol, and its use is indicated in children and haematological malignancy.

Further comments

The acute destruction of a large number of tumour cells is associated with metabolic chaos, and is called "tumour lysis syndrome". Cell destruction releases various intracellular chemicals into the circulation, some of which may effect profound complications. Electrolyte release causes transient hypercalcaemia, hyperphosphataemia and hyperkalaemia. The release of calcium and phosphate into the blood stream rarely causes any significant consequences. However, the calcium and phosphate may co-precipitate and cause some impairment of renal function. Nucleic acid breakdown leads to hyperuricaemia and this, unless treated appropriately, can be complicated by renal failure due to the precipitation of uric acid crystals in the renal tubular system.

Tumour lysis syndrome results from spontaneous or treatment-related apoptosis and usually occurs within 5 days of commencing chemotherapy and a number of factors are associated with it (see Table 1).

Bulky chemosensitive disease
Elevated pre-treatment serum uric acid
Elevated serum lactate dehydrogenase (LDH)
Poor renal function

Table 1 : Risk factors for the development of tumour lysis syndrome.

It is important to identify patients at risk of tumour lysis syndrome and institute prophylactic measures prior to commencement of treatment. These measures include allopurinol, intravenous fluids, urinary alkalinisation and rasburicase[5-7].

Note

Other oncological emergencies including neutropenic sepsis and hypercalcaemia of malignancy have been covered in previous Foundation Year Journal issues on haematology.

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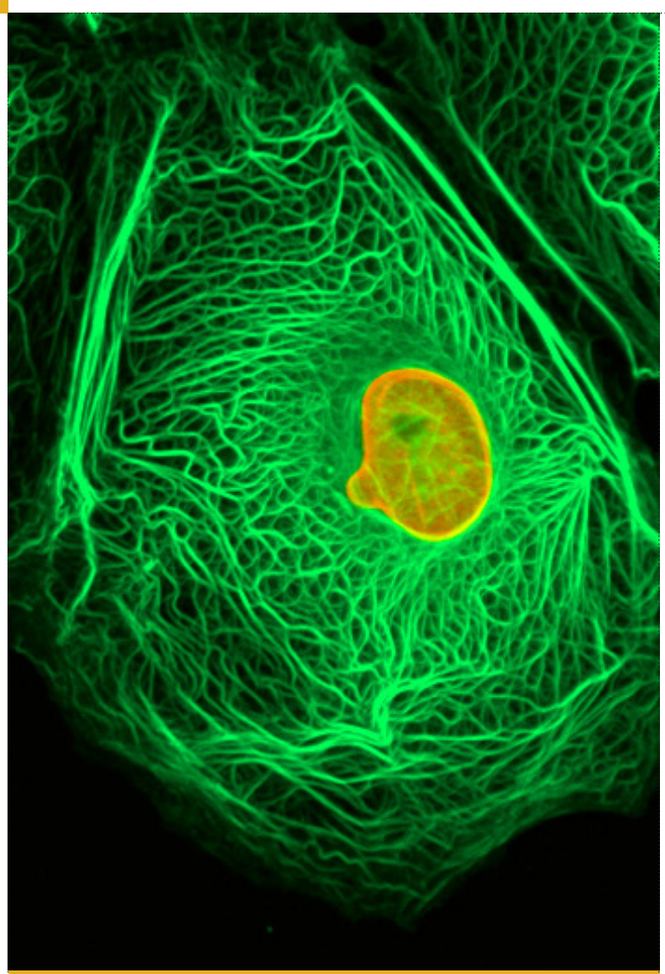
CANCER: TOP TEN TIPS FOR FOUNDATION DOCTORS

Karol Sikora



With one in three of us developing it. The abnormal growth process results in a very mixed bag of symptoms. Good Clinical Care.

1. Cancer is surprisingly common

With one in three of us developing it. The abnormal growth process results in a very mixed bag of symptoms. Always take a note of patients who keep coming back with progressively worsening symptoms arising from the same site in the body. Never ignore lumps and bumps unless you are sure they are benign. Weight loss, anorexia, localised pain and dyspnoea need to be taken seriously. Carry out a full examination and then request at least a FBC, LFTs, chest X-ray and urinalysis. If symptoms still persist refer on to an appropriate consultant.

There is still much controversy about the 2-week wait rule as 60% of all patients eventually found to have cancer do not meet the usual criteria. Fast tracking some simply slows down the journey for the majority. But it's a great political gesture for the voting public. The tragedy is that because of capacity problems subsequent delays downstream after being first seen usually obliterate any gain. In true Stalinist tradition, they are simply not counted by the NHS. There's no 2-week wait at all in Europe – it's all a next day service.

2. Increasingly patients want second opinions

When things are not going well. These are rarely of any value when there is metastatic cancer. The options are limited and once first line chemotherapy fails for most people with solid tumours it's mainly clutching at straws. But the rationing of new drugs and the inequity of their use – Scottish patients can access more drugs than those in England – leads to a not unreasonable mistrust in the system. Try persuading patients to talk to their treatment consultant, although time limitations in the NHS are a major problem. This is a lot simpler and cheaper than going to New York for another opinion. It is appropriate to ask for another view if some very drastic surgery or risky chemotherapy is being contemplated right at the start of treatment.

3. The saying that "no lady should have a lump in the breast" is still true.

The only exception is when the lump has been investigated and found to be definitely benign. Delays in the diagnosis of breast cancer are creating a burgeoning business for medical litigation lawyers. You don't need this hassle, so refer on early to a breast clinic. They are now very well organised and provide excellent service.

4. Increasingly men want a PSA test.

The current guidance – that after appropriate counselling men over 50 should be offered testing if they so choose – is a cop out. The difficulty is what to do with patients who have a mildly elevated PSA of between 4–6ug/L. Although many will actually have early cancer it may well never trouble them clinically and they will likely die with and not from their disease. No survival benefit from screening with PSA has ever been demonstrated despite its public appeal. We await more discriminatory tests which are on the way.

CANCER: TOP TEN TIPS FOR FOUNDATION DOCTORS

Karol Sikora

5. Patients take bleeding from an orifice seriously

especially if it persists. But even quite large abdominal masses, slow growing lymphadenopathy and persistent cough do not seem to ring the alarm bells. Always examine the patient before dismissing them as hypochondriacs. Never ignore a bleeding skin lesion that has been present for more than a month.

6. Dyspepsia is common and upper GI cancer is rare.

Sorting out the diagnosis is challenging and may be costly especially in the worried well who are often depressed and miserable. Weight loss, anorexia, change in bowel habit and fatigue should prompt investigation and referral. Persistence and progression of symptoms should be taken seriously.

7. People and their younger relatives seem to be increasingly avid for information.

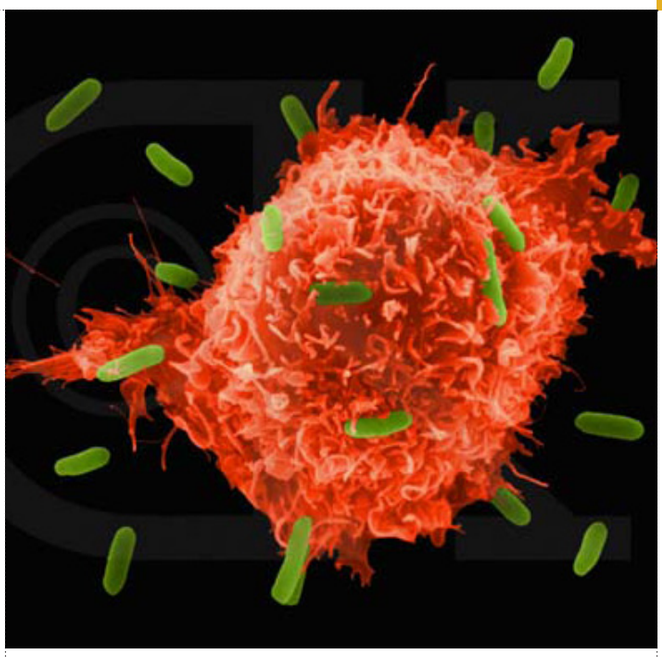
Don't try to stop the trend – you won't succeed. There are now over 300 million websites for cancer. Most are nonsense. The best three for your patients are: **www.macmillan.org.uk** the best information site for cancer patient; **www.cancerresearchuk.org.uk** Britain's largest cancer research charity; and the US National Cancer Institute in Washington **www.cancer.gov.** There are also a few good disease specific charities which run sites many find helpful.

8. Get to know your local palliative care team.

They can be incredibly useful in sorting out home care, hospice admission and respite care. Macmillan nurses and visiting home teams can deal with a lot more than pain. Most patients would choose to die at home but the backup has to be prepared well ahead. Local provision is enormously variable but usually very useful. Don't try to provide palliative care yourself. A Middlesbrough GP found himself in the dock for three counts of murder 2 years ago for giving rather old fashioned analgesics to elderly cancer patients. Luckily, he was acquitted. Modern palliative care is all about teamwork.

9. Alternative medicines are a difficult area for all of us.

While complementary therapies, such as massage, healing, Reiki, acupuncture and counselling, help patients to cope with their situation and improve their quality of life there is some pretty wacky stuff going on out there. This is often very pricy – on the same scale as high cost cancer drugs. Bizarre clinics in Germany seem to be getting away with more than £10,000 for a week's mumbo jumbo. But remove hope at your peril – you certainly won't be thanked for it. Penny Brohn Cancer Care in Bristol provides information and courses at very reasonable prices, www.pennybrohncancercare.org



10. Preventing cancer is a vital role for primary care.

It's difficult to sell to customers who like the media are obsessed with incredibly low risk causes, such as mobile phones, power lines and pesticides, while smoking, sex, sun and obesity are far more relevant. Why not give lifestyle advice to patients that seem to have major problems with smoking. Why not get your practice nurse to regularly advise patients while she checks blood pressure and syringes ears. Over the next few years there will be some nifty tests available to predict genetic risk. Coupled with effective risk biomarkers we could enter an era similar to the use of statins to reduce atherosclerosis with new drugs to avoid cancer. But motivating patients without cancer to do something about their lifestyle is actually very challenging indeed.

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WARD-BASED EMERGENCIES IN ONCOLOGY: NEUTROPAENIC SEPSIS; CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING; HYPERCALCAEMIA

Eleanor Jean Aynsley, Charles Kelly, Melanie Robertson and Sanjoy Chatterjee

Systemic chemotherapy is being used increasingly to treat malignant tumours. Good Clinical Care.

Systemic chemotherapy is being used increasingly to treat malignant tumours. With decentralisation of chemotherapy units, it is now increasingly important that doctors in training get experience in managing the common and serious toxicities secondary to chemotherapy. The following article aims to give an overview of some of the practical issues encountered in routine medical practice.

Neutropaenic sepsis can be life-threatening unless prompt and effective management is initiated; while chemotherapy-induced nausea and vomiting, and tumour-related hypercalcaemia can lead to significant morbidity although modern treatment regimes are usually effective in their treatment.

Neutropaenic sepsis

A full review of the management of febrile neutropaenia and confirmed neutropaenic sepsis is beyond the scope of this article, but the salient summary point useful for daily patient management is being outlined below.

Fever in patients post-chemotherapy can be a life-threatening[1] complication although in half the cases no obvious source of infection is found[2].

Neutropaenia is defined as decrease in peripheral neutrophils in peripheral blood[3]. It may be classified as being: mild (neutrophil count 1–2 x 10^9/L); moderate (0.5–1 x10^9/L); or severe (<0.5 x 10^9/L). The risk of neutropaenia is greatest at around 7–10 days after delivery of most systemic chemotherapy, but in some patients this may occur sooner or be prolonged therefore patients are encouraged to seek medical advice if they develop symptoms suggestive of infection at any stage of their chemotherapy cycle.

A recent systematic review[4] and the Cochrane review[1] have concluded that gram positive bacteria is a more common cause of infection in cancer patients.

Patients in whom neutropaenic sepsis is suspected must be assessed and treatment initiated urgently if the patient is moderately to severely neutropaenic and has any of the following:

- Pyrexia ≥38°C on a single reading.
- Pyrexia ≥37.5°C on two readings over an hour.
- Unexplained tachycardia or hypotension.
- Focal signs of infection.
- Generally unwell.

Management

If the patient manifests any of the above features, prompt treatment should be initiated. One should not wait for confirmatory laboratory results before initiating the treatment.

The bullet points summarises the treatment algorithm. This is just a guide and if in doubt appropriate senior support should be called for as soon as possible.

- Resuscitate if necessary. Often these patients suffer from respiratory tract infections and need airway support. If hypotensive, intravenous fluids should be used to support the patients circulation.
- Obtain venous access and take blood for full blood count (FBC), urea and electrolytes (U&Es), CRP.
- Take urgent blood cultures, both peripherally and from any central line.
- Treat immediately with broad spectrum antibiotics (see below).
- Take history and examine for focus of infection.
- Request MSU, stool culture, wound swabs, throat swabs.
- Request chest X-ray.
- Commence intravenous fluids if patient felt to be dehydrated, or is tachycardic or hypotensive. Hourly (or more frequent if unwell) observations (pulse, blood pressure, respiratory rate and temperature: used to calculate early warning score).
- Strict fluid balance, consider catheterisation to facilitate this if patient acutely unwell.
- Isolate, preferably in room with negative pressure ventilation.
- If unstable consider assessment for admission to ITU.

One must remember that patients with neutropaenic sepsis can quickly deteriorate.

Antibiotic guidelines

WARD-BASED EMERGENCIES IN ONCOLOGY: NEUTROPAENIC SEPSIS; CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING; HYPERCALCAEMIA

Eleanor Jean Aynsley, Charles Kelly, Melanie Robertson and Sanjoy Chatterjee

One must be familiarised with the local hospital policy, but a common schedule[2,5] used in the UK is a combination of tazocin (piperacillin + tazobactam) and gentamycin, with gentamycin given as stat dose if renal function is adequate. If allergic to penicillin: meropenem may be used. This drug is favoured in patients who have received potentially nephrotoxic chemotherapy, such as cisplatin. If the patient remains febrile after 48 hours and/or there is clinical deterioration discussion with the microbiology team is vital changing to second line antibiotics, which could include meropenem (may be indicated particularly if culture and sensitivity information is not available).

If blood cultures indicate a central line infection particularly of a skin tunnelled central catheter (Hickman line) consultation with the microbiology team and patients oncology teams is indicated as removal of the line is not always indicated unless the patient continues to deteriorate or specific bacteria are cultured. Antibiotics are usually continued until neutrophil counts are ≥0.5 x 10^9 and the patient have had a total of at least 5 days of intravenous antibiotics and has been afebrile for at least 48 hours.

Over the last few years there has been research and review[1, 4, 6] of the literature on the usage of antibiotics in neutropaenic patients. These have shown that oral antibiotics (quinolones and ampicillin/clavulanate were most commonly used oral antibiotics) can be used safely instead of intravenous antibiotics in non-leukaemic patients who are haemodynamically stable, without any evidence of soft tissue infection, pneumonia or infection of a central line[1].

Granulocyte colony stimulating factors (G-CSFs) can be used to prevent neutropaenia, and are most commonly used for secondary prophylaxis (i.e. after an episode of neutropaenic sepsis has occurred to prevent subsequent similar episodes post-chemotherapy).

In patients with febrile neutropaenia they are not routinely used, however, but could be considered (after discussion with a senior colleague) in certain patients at a high risk for complications as outlined below:

- Expected prolonged neutropaenia (>10 days).
- Profound (<0.1 x 10^9/L) neutropaenia.
- Age >65 years.
- Uncontrolled primary disease.
- Pneumonia.
- Hypotension and multi-organ dysfunction.
- Invasive fungal infection.
- Being hospitalised at the time of developing fever[5].

There is evidence[7] that G-CSF use reduces the length of grade 4 neutropaenia, antibiotic therapy and hospital stay although there are not many studies comparing antibiotic usage to that of G-CSF[8]. Although there is no clear evidence regarding survival benefit in using G-CSF in all febrile neutropaenic patients, in certain cancers like node positive breast cancers it may be used to improve dose density of the chemotherapy given that this may prolong survival[9].

Chemotherapy-induced nausea and vomiting (CINV)

This is a common side effect of chemotherapy and may be a cause of significant morbidity for patients if not managed adequately. Different chemotherapy regimens have varying rates of the risk of nausea and vomiting. Table 1 summarises the emetogenicity of common chemotherapies used in cancer care, however, modern chemotherapy regimes commonly uses combinations of two or more chemotherapy drugs thereby increasing the emetogenicity following a cycle of administered chemotherapy.

High risk of emesis (>90% risk of emesis)
• Cisplatin
• Cyclophosphamide >1500mg/m^2
• Streptozotocin
• Dacarbazine
Moderate risk (30–90%)
• Oxaliplatin
• Carboplatin
• Ifosfamide
• Cyclophosphamide <1500mg/m^2
• Doxorubicin
• Epirubicin
• Irinotecan
Low risk (10–30%)
• Paclitaxel
• Docetaxel
• Topotecan
• Etoposide
• Pemetrexed
• Methotrexate
• Mitomycin
• Gemcitabine
• Fluorouracil
Minimal (<10%)
• Bleomycin
• Vinca alkaloids[18]

Table1: Chemotherapy and their emetogenic potential[18].

WARD-BASED EMERGENCIES IN ONCOLOGY: NEUTROPAENIC SEPSIS; CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING; HYPERCALCAEMIA

Eleanor Jean Aynsley, Charles Kelly, Melanie Robertson and Sanjoy Chatterjee

An increased risk of emesis is present if the patient has:

- Previous poor control of nausea and vomiting.
- A history of motion sickness.
- Being of a younger age.
- Being female.
- Having a chronic low alcohol intake[10].

Emesis post-chemotherapy may be acute (occurs during or following chemotherapy, up to 24-hours post and is mediated via the central vomiting centre); delayed (most known with cisplatin, but can occur with other chemotherapy drugs, occurring 24–72 hours after chemotherapy, but can last up to a week) or anticipatory (occurs before and during chemotherapy, and is mostly related to psychological influences from previous experiences of vomiting)[11].

Management

For high-risk chemotherapy regimes: standard anti-emetics in the UK for high-risk chemotherapy are intravenous 5-HT3 antagonists, such as ondansetron (which works in the gastrointestinal tract (GIT) and central nervous system (CNS)[11] and dexamethasone prior to chemotherapy. Patients may then receive ondansetron orally for a further 48 hours and dexamethasone for 24 hours, with metoclopramide available if required (works directly on the GIT)[11].

For moderate-risk chemotherapy regimes: pre-chemotherapy the anti-emetic regime is usually the same as above, while post-treatment some centres give the same oral combination as above whereas others prescribe just dexamethasone with metoclopramide as and when needed.

For low-risk chemotherapy regimes: metoclopramide is prescribed pre-chemotherapy and then as and when needed.

For anticipatory nausea and vomiting, lorazepam may be prescribed for the evening before and the morning of chemotherapy

Second line anti-emetics

For highly emetogenic chemotherapy (like cisplatin-containing regimens) aprepitant (neurokinin-1 receptor antagonist)[11] may be added to the 5-HT3 and dexamethasone combination, in a dose of 125mg, 1 hour pre-chemotherapy and 80mg OD for 2 days. Recent evidence suggests that its addition improves the complete response rates of CINV[12].

Delayed nausea and vomiting: consider extending the routine anti-emetics (e.g. ondansetron) to 5 days and dexamethasone to 3 days, or palonosetron[13] pre-chemotherapy (long-acting 5-HT3 antagonist) along with dexamethasone may be used.

Other anti-emetics that are used include cyclizine (instead of metoclopramide) or haloperidol (antipsychotic)[11]. In cases of refractory vomiting, cyclizine or levomepromazine (antipsychotic)[11] may be used in combination with other anti-emetics, subcutaneously via a syringe driver. The management of a patient that attends hospital with acute nausea and/or vomiting following chemotherapy should initially be centred around ensuring the prescribed anti-emetic regimen is being effectively administered, problems may have occurred if the patient feels too nauseated to swallow oral tablets or indeed has vomited immediately following administration; changing anti-emetics to intravenous or sub-lingual may help. Dehydration may be a consequence of severe nausea or vomiting and assessment of whether intravenous fluid rehydration is required will also be needed. The hospital palliative care team should be contacted early in difficult cases of CINV.

Cancer-induced hypercalcaemia (CIH)

Hypercalcaemia (i.e. over 2.65mmol/L) is a relatively common metabolic emergency in cancer, occurring in approximately 5–30% of cancer patients during the course of their disease. CIH is most commonly seen in patients with breast cancer, non-small cell lung cancer and myeloma.

Presentation

This varies depending on the rate of the rise and the aetiology of hypercalcaemia. The classical symptoms was described by Maldonado as "bones, stones, groans and psychic moans". Some commonly encountered clinical features include constipation, nausea, confusion, changes in personality, increased thirst and diuresis leading to renal impairment. In extreme situations renal stone formation (more common if hypercalcaemia is due to primary hyperparathyroidism), arrhythmias and seizures may be encountered.

Aetiology of CIH

- *Humoral hypercalcaemia of malignancy:* raised PTHrP is the most common humoral regulator of CIH with some series[14] suggesting that up to 80% of patients with CIH have raised PTHrP (parathyroid hormone-related protein) levels. Raised PTHrP is common in squamous cell cancer (e.g. of lung or head and neck), breast cancer and renal cancer. This protein is produced by cancer cells and stimulates adenylate cyclase in kidney and bone, increasing osteoclastic bone resorption and tubular re-absorption of calcium.
- *Extensive osteolytic hypercalcaemia:* occurs where there are extensive bone metastases (e.g. in breast cancer) due to increased calcium release from the bone due to the effect of cancer cells on osteoclasts, but also due to the effect of humoral agents: cytokines; chemokines; and PTHrP[15].
- *Ectopic hyperparathyroidism:* rarely a cause of CIH.

WARD-BASED EMERGENCIES IN ONCOLOGY: NEUTROPAENIC SEPSIS; CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING; HYPERCALCAEMIA

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Treatment

Is essentially supportive and measures must be taken to improve the quality of life. Some of the important measures are summarised below:

- **Hydration:** with intravenous fluids, with monitoring of fluid balance, is important to increase urinary calcium excretion and restore glomerular function.
- **Bisphosphonates:** for example, zoledronic acid 4mg intravenously, following hydration work by inhibiting bone resorption by osteoclasts and are very good at lowering serum calcium, but can take 2–4 days to have their effect.
- **Other treatments:** rarely used since the development of potent bisphosphonates but sometimes useful: corticosteroids (decrease gastrointestinal absorption and inhibit bone resorption); diuretics (inhibit renal tubular calcium reabsorption); calcitonin (inhibits renal reabsorption and osteoclast resorption, and works rapidly so still useful to lower calcium, although its effect is short lived).
- **Anti-tumour treatment:** depending on the mechanism of the hypercalcaemia, can be useful[16, 17].

Conclusion

In most cases, by following the simple principles of management, significant complications of cancer and treatment-related side effects can be prevented. A lack of understanding of these important oncological situations can lead to serious and potentially life-threatening complications. Neutropaenic sepsis can lead to a fatal event within a short space of time, but such events can usually be prevented with prompt intervention. CINV and CIH can be morbid and inadequate management can lead to tremendous suffering and morbidity in these patients. It is extremely important to understand that most acute hospitals have set guidelines for managing these common problems and it is extremely important that Foundation Year doctors be very well rehearsed with these guidelines and in cases of doubt ask for advice from senior colleagues.

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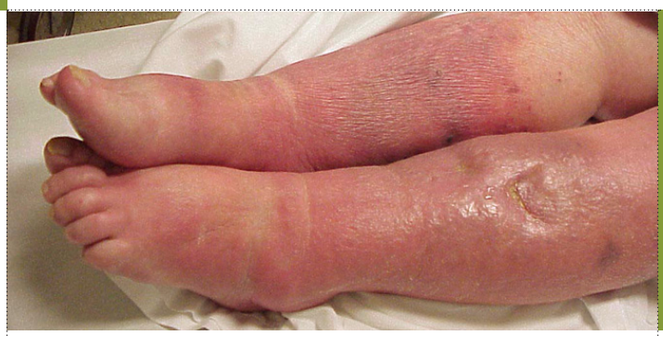
AN AUDIT OF TIMELY AND APPROPRIATE PRESCRIBING OF ANTIBIOTICS FOR PATIENTS WITH NEUTROPAENIC SEPSIS

Elizabeth Hood, George Madden, Gurjeet Pamma and Simon Grumett



Neutropaenic sepsis.
Good Medical Practice.

Abstract

Introduction

Mortality from neutropaenic sepsis is high if there are delays in diagnosis and initiation of treatment. The primary aim of this audit was to assess whether the location and timing of diagnosis for patients with new onset febrile neutropaenia and neutropaenic sepsis affected the likelihood of receiving appropriate protocol antibiotics.

Methods

Over a 6-month period, some 52 neutropaenic patients were identified as being admitted to a specialist oncology unit. Location of diagnosis related to whether oncology teams were the first contact teams or not at the time of diagnosis. Groups were compared with Chi-squared tests.

Results

A significantly greater proportion of patients where oncology teams were the first contact had correct protocol antibiotics prescribed (74% versus 42%, p=0.036). When considering the time of diagnosis to be within normal working hours or outside of working hours, there is no significant difference between the rate of appropriate prescribing (61% and 74% respectively, p=0.320).

There was a trend towards a higher proportion of inappropriate antibiotics in those who died compared to those who survived to discharge, although this failed to reach significance (57% (n=4/11) versus 26% (n=11/43) respectively, p=0.109).

Conclusion

Patients with neutropaenic sepsis are less likely to receive protocol antibiotics if they are assessed initially in acute medical or A&E areas, as opposed to specialist oncology units. Patients without protocol antibiotics may be at a higher risk of mortality. Measures have been taken to improve the knowledge of protocol antibiotics in non-specialist areas and prescribing regimes have been made widely available.

Introduction

Neutropaenic sepsis is the most common life-threatening complication of chemotherapy[1]. Mortality rates are high if there are excessive delays in diagnosis and the initiation of treatment; undiagnosed neutropaenic sepsis has a mortality rate of 20–30%[2]. The gold standard for the management of neutropaenia is protocol antibiotics prescribed and administered within 1 hour of diagnosis, which are timentin and gentamicin intravenously as first line for neutropaenic febrile and septic patients[3-6]. Those that are neutropaenic without signs of infection and are considered low risk may be treated with oral antibiotics[7-9]. Blood cultures should also be sent prior to the first antibiotic dose, with adjustments made depending on sensitivity[10].

The primary aim of this audit was to assess whether the location and timing of diagnosis for patients with new onset neutropaenia affected the likelihood of patients receiving appropriate protocol antibiotics.

Methods

Blood tests in all patients who were admitted to a combined oncology/haematology unit over a 6-month period were reviewed to identify those admitted with new onset neutropaenia. Neutropaenia was defined as a neutrophil count of less than 1.0 x 10^9/L. Patients were considered febrile if a temperature of 38°C or higher was recorded. Septic patients were identified by features of pyrexia plus tachycardia or hypotension[11]. Medical notes were reviewed to assess the time and location of diagnosis and the treatment received.

Location of diagnosis related to whether oncology teams where the first contact teams or not. The chemotherapy unit, oncology wards and oncology clinics were considered to be primary oncology areas, where A&E and medical admission units (MAU) were considered to be non-oncology areas. Time of presentation was classed as either within working hours (09.00 to 17.30 Monday to Friday), outside of working hours in a normal week (17.30–09.00 Monday to Friday) or over the weekend (09.00 Saturday to 09.00 Monday).

Groups were compared with Chi-squared tests or Fisher's exact tests as appropriate. Data was analysed using SPSS 16.0 (SPSS Inc, Chicago, Illinois).

AN AUDIT OF TIMELY AND APPROPRIATE PRESCRIBING OF ANTIBIOTICS FOR PATIENTS WITH NEUTROPAENIC SEPSIS

Elizabeth Hood, George Madden, Gurjeet Pamma and Simon Grumett

Results

Some 52 neutropaenic patients were identified: 56% (n=29) were male and 44% (n=23) were female, with an overall mean age of 61 years. Patients included 37% (n=19) who were neutropaenic without signs of infection, 34% (n=18) were febrile and 29% (n=15) who met the criteria for sepsis.

Overall 67% of neutropaenic patients were treated with the hospital protocol antibiotic regimes, leaving 33% of patients treated with antibiotics other than those which were recommended. Ten per cent of patients died prior to discharge (n=5).

Figure 1 shows that a significantly greater proportion of patients where oncology teams were the first contact had correct antibiotics prescribed (74% versus 42%, p=0.036); 34% of patients were diagnosed in the chemotherapy day case unit; 28% as ward inpatients; 15% in the A&E; 9% in the MAU; 12% from clinic; and 2% (n=1) were unknown.

Figure 2 shows the timing of diagnosis. When groups are combined to show those in normal working hours and out of working hours (nights and weekends), there is no significant difference between the rate of prescribing protocol antibiotics (61% appropriate within hours, 74% appropriate out of hours, p=0.320).

In terms of outcome, there was a trend towards a higher proportion of inappropriate antibiotics in those who died compared to those who survived to discharge, although this failed to reach significance (57% (n=4/7) inappropriate in those who died; 26% (n=11/43) inappropriate in those who survived, (p=0.109)). The outcome of two patients was unknown.

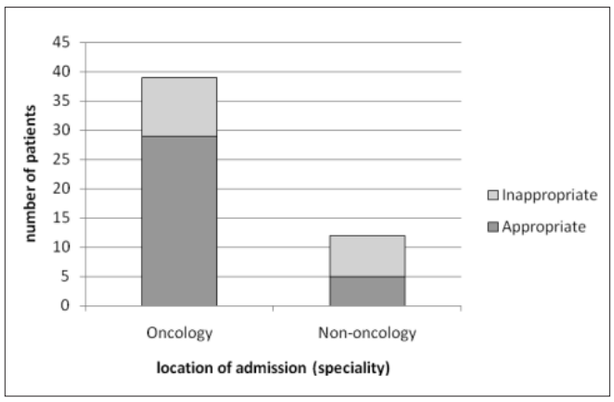


Figure 1: The place where first contact was made.

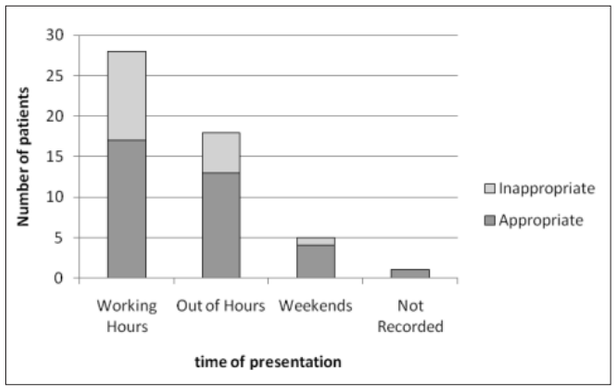


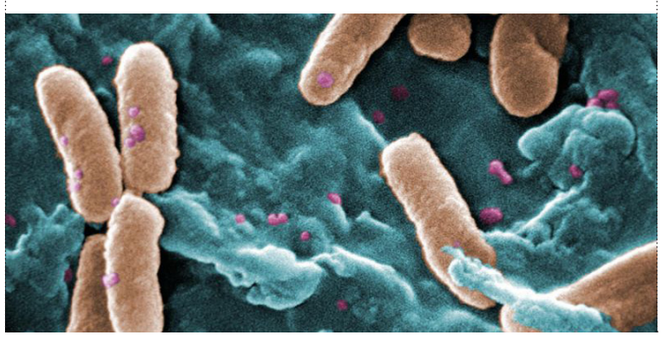
Figure 2: Time when diagnosed.

Discussion

When patients with new neutropaenia are first assessed, teams working in specialised oncology areas (i.e. chemotherapy units and oncology wards) are more likely to prescribe the gold standard protocol antibiotics compared to those assessed in acute medical areas (i.e. A&E and MAU). However, both teams did not achieve complete compliance, falling short of this gold standard.

Patients who are undergoing chemotherapy for a malignancy are at risk of becoming neutropaenic over the following days and weeks after treatment. Neutrophil levels of less than 2.0 x 10^9/L are abnormal and the patient becomes at risk when levels fall below 1.0 x 10^9/L[10]. The principles of managing chemotherapy induced neutropaenia are reducing the dose intensity of the chemotherapy and using protocol antibiotics[12].

The timing of diagnosis of neutropaenia did not affect outcome but the location of diagnosis did. Unspecialised, acute medical department and A&E were significantly worse at prescribing protocol antibiotics. The most likely explanation for this is a lack of awareness by resident teams of the antibiotic prescribing protocol. This is in contrast to specialist oncology teams and doctors, who are more likely to deal with these patients on a daily basis, may have more immediate availability of printed guidelines and have undergone specific departmental induction. Furthermore, chemotherapy inpatients have specific red alert cards placed into their notes, which alerts oncology teams to the risk of neutropaenia; this is a source of bias.



AN AUDIT OF TIMELY AND APPROPRIATE PRESCRIBING OF ANTIBIOTICS FOR PATIENTS WITH NEUTROPAENIC SEPSIS

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There was a trend in this study that within those who died, there was a higher proportion of non-protocol antibiotics. This suggests that the prescription of protocol antibiotics may influence survival, and hence the importance of this topic. However, the authors recognise that there are many other factors influencing mortality, which were beyond the scope of this audit. Nevertheless, it is known that mortality from neutropaenic sepsis is high if there are delays in diagnosis and the initiation of appropriate treatment[13].

Recommendations

Changes as a result of this audit primarily include clarification in guidance for junior doctors working in acute areas in the initial management of neutropaenic sepsis. A single, specific document is now available on the trust intranet and prescribing for these patients is summarised in departmental inductions. This includes the oncology unit, in an aim to improve compliance there too. Furthermore, specific education and training into the management of neutropaenic sepsis is imparted to the wider multidisciplinary team, including key nurses, in order to provide further depth of knowledge regarding the need for protocol antibiotics. Patients are educated to inform the doctor they first come into contact with that they have been receiving chemotherapy and are at risk of "low blood counts". One year on the current Foundation Years doctors have re-audited the project thereby closing the audit cycle.

Conclusions

Patients with neutropaenic sepsis are less likely to receive protocol antibiotics if they are assessed initially in acute medical or A&E areas, as opposed to specialist oncology units. Patients without protocol antibiotics may be at a higher risk of mortality. Measures have been taken to improve the knowledge of protocol antibiotics and prescribing regimes have been made more widely and visibly available.

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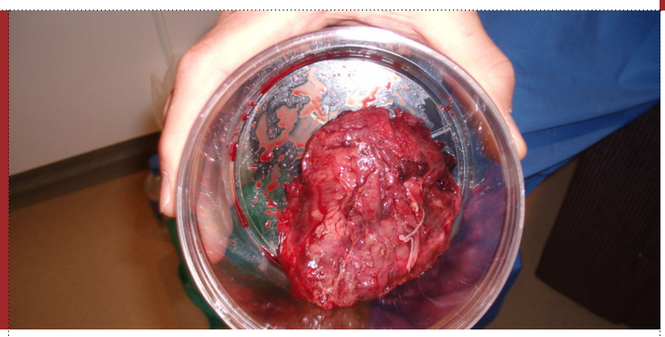
RECOGNITION AND MANAGEMENT OF TUMOUR LYSIS SYNDROME

Jennifer A Bradbury and Judith Cave

Tumour lysis syndrome is a potential complication of chemotherapy, and occurs due to extensive cellular breakdown in patients with bulky, rapidly proliferating and highly treatment-sensitive tumours.
Patient Management.



Abstract

Tumour lysis syndrome is a potential complication of chemotherapy, and occurs due to extensive cellular breakdown in patients with bulky, rapidly proliferating and highly treatment-sensitive tumours[1]. It results in the release of intracellular contents into the circulation, and may lead to metabolic disturbance, renal failure and cardiac arrhythmias.

This article will focus on the case of a patient who developed tumour lysis syndrome during treatment for Burkitt's lymphoma. It will aim to highlight the identification of high-risk patients, strategies for prevention, and treatment of the metabolic and renal complications.

Case History

A 32-year-old male patient of Asian origin presented with a 3-week history of lethargy, night sweats and abdominal distension. On examination he had no palpable lymphadenopathy, his chest was clear and he had moderate ascites. Initial blood tests revealed haemoglobin 152g/l, Total white cell count 10.9 x 10^9/L, platelets 521 x 10^9/L, lactate dehydrogenase (LDH) 2208iu/L, urea 9.8mmol/L, creatinine $10^6{}_{mu}$mol/L and urate 0.63mmol/L. CT imaging showed extensive peritoneal disease with diffuse soft tissue encasement of the bowel, ascites and bilateral pleural effusions. A peritoneal biopsy confirmed the diagnosis of Burkitt's lymphoma. Bone marrow biopsy showed no evidence of involvement by lymphoma.

The patient was commenced on chemotherapy with R-CODOX-M (cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate with rituximab)/IVAC (ifosfamide, etoposide and high-dose cytarabine). This is an alternating combination chemotherapy regimen containing multiple effective drugs and is the current standard therapy for the majority of cases of Burkitt's lymphoma.

Intravenous rehydration was started 24 hours prior to initiation of chemotherapy with 4L/day. Potassium was not added to the intravenous fluids unless the serum potassium fell below 3.0mmol/L. The patient received allopurinol 300mg daily and a single dose of rasburicase at a dose of 200micrograms per kilogram as prophylaxis against tumour lysis syndrome. His renal function, urate, phosphate and calcium were to be monitored twice daily.

On day 3, the patient's serum phosphate level rose to 2.2mmol/L. Intravenous hydration and accurate fluid balance monitoring were continued. His renal function, serum urate, phosphate and calcium were monitored 6 hourly.

On day 4 the patient became oliguric (<15mls/hr). Clinical assessment revealed blood pressure 125/85, pulse 113bpm (sinus rhythm), jugular venous pressure elevated by 4cm, bilateral pleural effusions, ascites and peripheral oedema. His renal function deteriorated and he developed hyperkalaemia, hyperphosphataemia and hypocalcaemia:

Urea	**32.7mmol/L**
Creatinine	**197_{mu}mol/L**
Potassium	**5.26mmol/L**
Phosphate	**6.25mmol/L**
Calcium	**1.63mmol/L**
Urate	**0.37mmol/L**

In view of persistent hyperphosphataemia and fluid overload, the patient was transferred to the Intensive Care Unit for haemofiltration. In this setting he also underwent continuous cardiac monitoring for potentially life-threatening arrhythmias. Haemofiltration was continued for 3 days, after which the patient's serum phosphate level had normalised although his renal function had deteriorated further. Over the following 14 days, his renal function gradually normalised.

The patient is now in complete radiological remission after completing a total of 4 cycles of chemotherapy with R-CODOX-M/IVAC.

Discussion

Tumour lysis syndrome is a group of metabolic derangements caused by massive and abrupt lysis of malignant cells. It may occur spontaneously, but usually develops after the initiation of treatment in the form of chemotherapy. Hyperkalaemia and hyperphosphataemia occur as a direct result of cell lysis. Initially, the kidneys are able to compensate for the increased serum levels of phosphate through increased excretion and decreased tubular re-absorption of phosphate[2]. However, renal elimination mechanisms are eventually overwhelmed and serum phosphate levels rise. The rapid release and metabolism of intracellular purine nucleic acids leads to the production of urate, causing hyperuricaemia. Urate is soluble in plasma and normally excreted through the kidneys. It is less soluble in the normally acidic environment of the renal tubular fluid, thus increasing the possibility of the formation of uric acid crystals in the case of hyperuricaemia[3].

RECOGNITION AND MANAGEMENT OF TUMOUR LYSIS SYNDROME

Jennifer A Bradbury and Judith Cave

Renal failure in tumour lysis syndrome occurs due to the combination of uric acid crystal nephropathy and the precipitation of phosphate with calcium in the renal tubules, leading to an acute obstructive nephropathy.[2,4] Hypocalcaemia occurs as a result of precipitation with phosphate. Hyperkalaemia is exacerbated by the inability of the kidneys to excrete the potassium load released through tumour cell lysis[4] This leads to an increased risk of cardiac arrhythmias.

Patients are considered to be at high risk of tumour lysis syndrome if they have tumours such as Burkitt's lymphoma and acute leukaemia, which often respond rapidly to chemotherapy[4]. Other risk factors are elevated LDH levels, which are often associated with rapidly proliferating and hence rapidly responding tumours, and bulky disease, which raises the risk of significant lysis[1,5].

Co-morbidities, such as pre-existing renal impairment or volume depletion, may also put the patient at an increased risk of developing tumour lysis syndrome. Patients considered at high risk should receive prophylaxis against tumour lysis syndrome in the form of intravenous hydration, allopurinol and rasburicase.

Allopurinol is an inhibitor of xanthine oxidase, which is the enzyme that is responsible for urate synthesis. Rasburicase is a recombinant form of the enzyme urate oxidase, which oxidises uric acid to allantoin, which is more soluble in urine than uric acid. Both drugs help to prevent and control hyperuricaemia and the risk of urate nephropathy. A randomized controlled trial was conducted comparing allopurinol to rasburicase in 52 paediatric patients with leukaemia or lymphoma at high risk of tumour lysis syndrome[6]. For patients randomized to rasburicase, there was an 86% reduction in plasma urate levels within 4 hours of drug administration compared to only 12% for allopurinol ($P<0.001$). The rasburicase group experienced a 2.6 fold decrease in urate exposure compared with the allopurinol group.

Close monitoring of urine output with fluid rehydration to maintain urine output >0.5ml/kg is also essential prophylaxis, as oliguria predisposes to the renal deposition of uric acid crystals. Urine alkalinisation with sodium bicarbonate, aiming for a pH of >7, in order to increase urate solubility has traditionally been standard practice. However, alkalinisatio n may have some drawbacks, such as increasing the likelihood of calcium phosphate precipitation in the renal tubules[5]. It is now less widely used as part of tumour lysis syndrome management, particularly since rasburicase has been introduced[7].

Hyperkalaemia should be managed according to standard measures. Treatment of asymptomatic hypocalcaemia is not usually recommended as this may increase the risk of calcium phosphate precipitation and obstructive nephropathy[5].

Deteriorating renal function in a patient on chemotherapy needs thorough clinical assessment to establish the cause. Table 1 lists the potential differential diagnosis to be considered in such a patient.

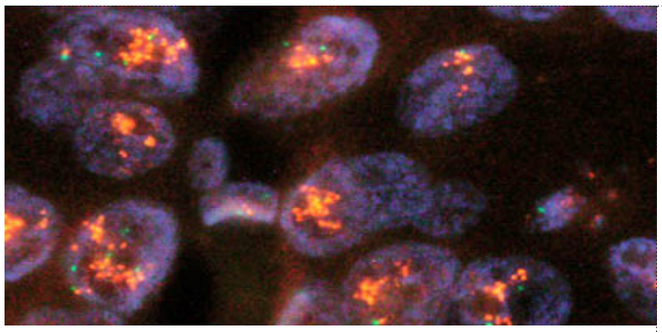
	Cause	Signs
Pre-renal	Hypovolaemia e.g. secondary to chemotherapy-induced vomiting, diarrhoea or malignant bowel obstruction.	Signs of hypovolaemia e.g. dry mucous membranes, JVP not visualised, hypotension, tachycardia, oliguria
	Sepsis e.g. neutropenic sepsis	As above, plus fever. May have warm vasodilated peripheries, may be peripherally shutdown.
Renal	Drug-induced e.g. chemotherapy, CT contrast, NSAIDs, aminoglycoside antibiotics.	No clinical evidence of hypovolaemia. May become fluid-overloaded. Possibly oliguria.
	Tumour lysis syndrome	
	Hypercalcaemia	
	Immunoglobulin light chain deposition, amyloid and hypercalcaemia in myeloma.	
	Hepato-renal syndrome	
	Nephrotic syndrome secondary to malignancy.	
Post-renal	Obstruction, either ureteric or bladder outflow tract e.g. due to pelvic or retroperitoneal tumour.	Possibly signs of fluid overload e.g. raised JVP, peripheral oedema. Oliguria. Palpable bladder.

Table 1: Differential diagnosis of renal failure in a patient on chemotherapy

The combination of acute renal failure in the context of hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia is sufficient to establish the diagnosis of tumour lysis syndrome.

RECOGNITION AND MANAGEMENT OF TUMOUR LYSIS SYNDROME

Jennifer A Bradbury and Judith Cave



If the previously mentioned measures for the management of tumour lysis syndrome fail, it is important to consider the need for dialysis or haemofiltration. Indications for dialysis include fluid overload, symptomatic uraemia (pericarditis, encephalopathy), persistent hyperkalaemia or hyperphosphataemia, symptomatic hypocalcaemia and severe metabolic acidosis[5].

Multiple Choice Questions

1. Which of the following is a typical metabolic abnormality occurring in tumour lysis syndrome?

a. Hypophosphataemia.
b. Hypokalaemia.
c. Hypercalcaemia.
d. Hyperuricaemia.
e. Metabolic alkalosis.

2. Which of the following types of malignant disorder is unlikely to be associated with tumour lysis syndrome on induction of chemotherapy?

a. Small cell lung cancer.
b. Metastatic melanoma.
c. Metastatic teratoma.
d. High-grade non-Hodgkin's lymphoma.
e. Acute lymphoblastic leukaemia.

Answers

1. d. Hyperuricaemia. This is a characteristic feature of the rapid breakdown of large numbers of cells which occurs with chemotherapy in highly sensitive tumours. The other typical metabolic features of the syndrome are hyperphosphataemia, hyperkalaemia, hypocalcaemia and a metabolic acidosis in association with renal failure.

2. b. Metastatic melanoma. Tumour lysis syndrome usually occurs in patients with tumours which have high proliferative rates and which are highly sensitive to chemotherapy. The highest risk of developing tumour lysis syndrome is observed in acute leukaemias and in high-grade non-Hodgkin's lymphomas. It has also been reported in patients with solid tumours such as metastatic teratoma and small cell lung cancer. Melanoma is not particularly sensitive to chemotherapy and therefore treatment is unlikely to lead to the development of tumour lysis syndrome.

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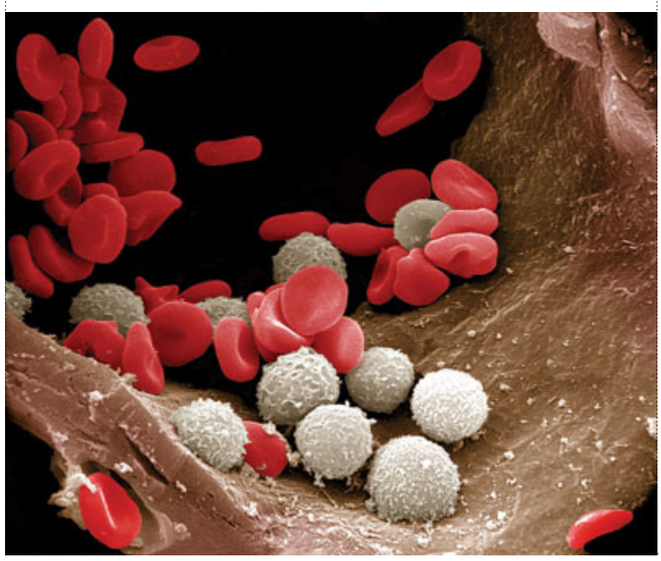
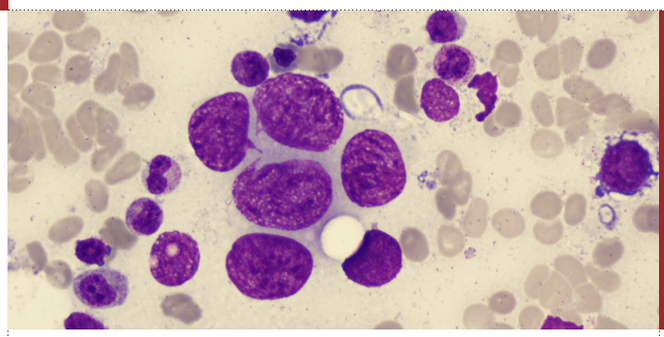


METASTATIC CARCINOMA OF UNKNOWN PRIMARY- CASE BASED DISCUSSION

Daniel Krell



Metastatic carcinoma of unknown primary (CUP) accounts for 2–4% of all malignancies. Patient Management.

Abstract

Metastatic carcinoma of unknown primary (CUP) accounts for 2–4% of all malignancies. Patients present with metastatic disease, but despite standard investigations, the primary site often cannot be located. The prognosis is poor, except in a few specific subgroups, and response to chemotherapy remains disappointing. Patients often initially present with symptoms of metastatic cancer to their GP or A&E and are admitted to hospital under acute medical or surgical teams for investigation, before being referred to oncology services for treatment once a diagnosis has been made.

This case-based discussion illustrates a typical case of a patient who presents with CUP and outlines the process by which the patient should be investigated, and referred to the oncology services. The importance of involving multidisciplinary team members is highlighted and the process of breaking bad news is discussed. The use of novel molecular diagnostic techniques is also described.

Case history

A 57-year-old man presented as an emergency to his local A&E department with a 3-week history of abdominal pain, nausea and weight loss. On clinical examination he was noted to be cachectic, with 2cm tender hepatomegally and moderate ascites. His WHO performance status was 1 (see Table 1).

0	Asymptomatic (fully active, able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work))
2	Symptomatic, <50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

Table 1: WHO performance status.

His LFTs were mildly deranged: bilirubin 11umol/L (<21); ALP 160U/L (35–129); ALT 40U/L (<31). He was mildly dehydrated: urea 9mmol/L (2.1–7.1); Cr 80µmol/L (49–92). FBC, clotting and electrolytes were normal. He was admitted under the on-call medical team.

He was rehydrated with IV fluids and given paracetamol and tramadol as analgesia, and cyclizine as an anti-emetic. A liver ultrasound scan and CT chest, abdomen, pelvis were arranged which showed multiple liver and lung metastases (see Figure 1).

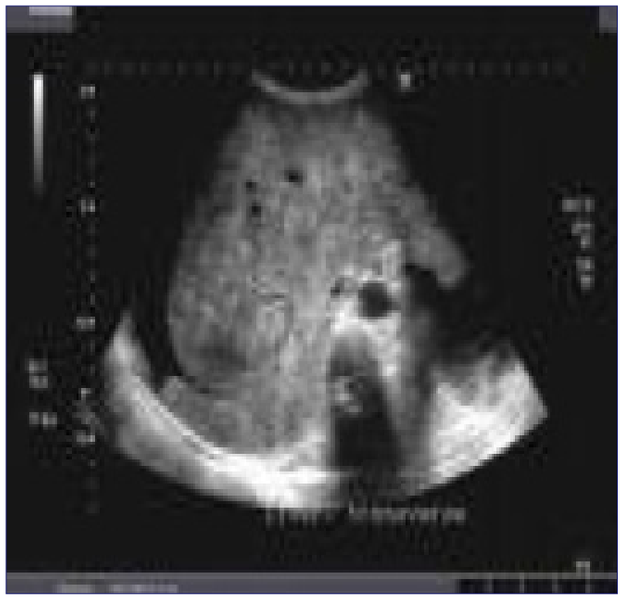


Figure 1: Ultrasound scan image showing liver metastases.

He subsequently had an ultrasound guided liver biopsy, which showed metastatic adenocarcinoma. Immunohistochemical analysis was positive for CEA and CK7, and negative for CK20 and was reported as a likely metastasis from a gastro-oesophageal primary. However, upper GI endoscopy, colonoscopy and a dedicated pancreatic CT scan were unable to locate the primary tumour. The patient was informed of the diagnosis of metastatic adenocarcinoma of unknown primary by the medical registrar and upper GI clinical nurse specialist and was told he was to be referred to the oncology team. He was also referred to the hospital and community palliative care teams, who provided symptom control advice and psychosocial support.

METASTATIC CARCINOMA OF UNKNOWN PRIMARY- CASE BASED DISCUSSION

Daniel Krell

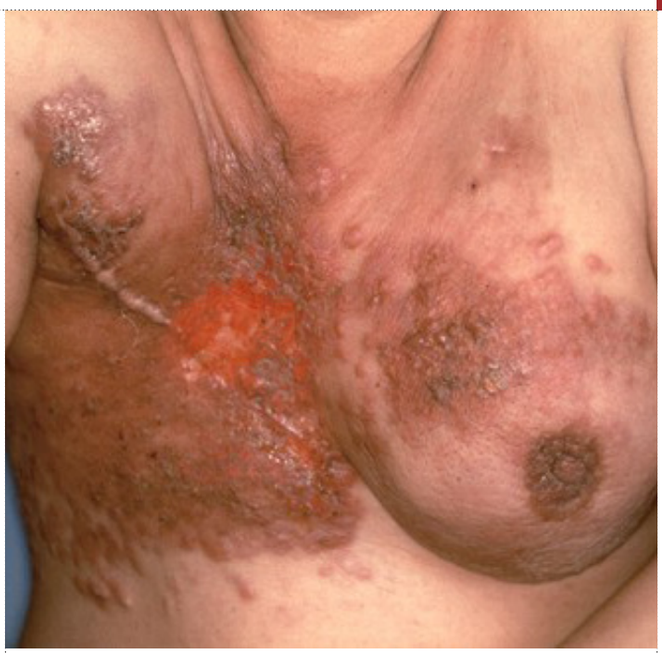
His case was discussed at the upper GI oncology MDT, where an oncology outpatient appointment was arranged. His symptoms were now controlled and he was discharged from hospital having been referred to his local community Macmillan team for support.

He was seen in the oncology clinic the following week. The oncologist explained that he had metastatic adenocarcinoma but that despite a full array of radiological and endoscopic investigations, the primary site remained unclear. He was advised to commence palliative chemotherapy with epirubicin, cisplatin and capecitabine (ECX), directed against gastro-oesophageal cancer, on the basis of the histology result. The intended benefits and potential side effects were explained and he signed a consent form agreeing to treatment (see Table 2).

A CT scan following 3 months of ECX chemotherapy demonstrated a partial response to treatment. However, unfortunately a repeat CT scan after 6-months treatment showed progressive disease. He was therefore offered irinotecan as second line chemotherapy for gastro-oesophageal cancer. He asked if there were any other management options and was offered the opportunity to self-fund the molecular analysis of his liver biopsy using the commercial CupPrint® test. It was explained that the appropriate chemotherapy regimen would then be offered based on the result. He opted for the latter. The CupPrint® test suggested that the primary tumour was a cholangiocarcinoma. Consequently he commenced second line chemotherapy with gemcitabine. After 5 months of gemcitabine chemotherapy his disease progressed. His performance status reduced to WHO grade 3 and he developed recurrent ascites and jaundice. Chemotherapy was discontinued. The decision was made to shift the focus of care from active management to symptom control, and this was undertaken with the assistance of the community palliative care services and his local hospice.

Benefits	Side effects
Reduced tumour-related symptoms	Hair loss
Improved quality of life	Nausea and vomiting
Increased progression free survival	Neutropaenic infection
	Cardiac toxicity
	Renal toxicity
	Diarrhoea
	Mucositis
	Hand-foot syndrome

Table 2: Benefits and side effects of ECX chemotherapy in a patient with metastatic adenocarcinoma of unknown primary.



Introduction

Carcinoma of unknown primary (CUP) represents a group of heterogeneous tumours, which present with metastatic disease for which, despite standard investigations, the primary site cannot be found.

CUP accounts for 2–4% of all malignancies6 and despite improving diagnostic tools, it remains a common clinical problem. Histologically the vast majority of cases are adenocarcinoma (40–50%) and poorly differentiated carcinoma (30–40%)[5].

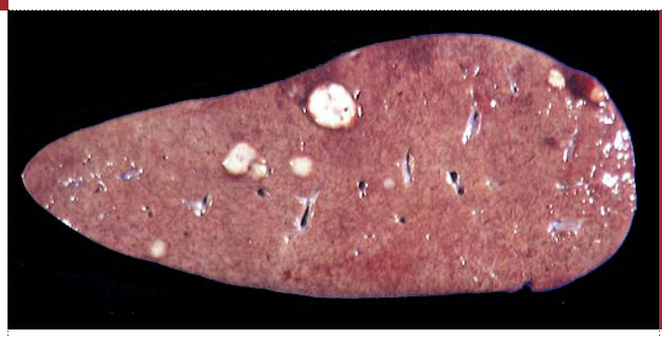
CUP is associated with a median survival of 6–8 months[9]. This is poor and significantly less than the expected survival for patients with a confirmed primary, following standard therapy.

CUP is generally treated with platinum/taxane-based combination chemotherapy, although cisplatin/gemcitabine combinations have also been shown to be effective[2]. Response rates are, however, disappointing (20–30%)[4] and treatment should be considered palliative.

There are, however, subgroups of patients who present with CUP that may be treated with tumour-specific chemotherapy, with an expectation of a significantly improved survival or in some cases cure (see Table 3). Unfortunately these subgroups represent only 5–10% of cases[8]. In cases where poorly differentiated tumours are reported, immunohistochemistry should be performed to specifically exclude a chemosensitive primary such as lymphoma or germ cell tumour.

METASTATIC CARCINOMA OF UNKNOWN PRIMARY- CASE BASED DISCUSSION

Daniel Krell



Metastatic carcinoma.
Patient Management.

Presenting Features	Tumour Specific Treatment
Peritoneal carcinomatosis in women	Ovarian cancer protocols
Malignant ascites in women	Ovarian cancer protocols
Axillary lymph node metastases in women	Breast cancer protocols
Osteoblastic bone metastases in males	Prostate cancer hormone manipulation protocols
Undifferentiated carcinoma involving retroperitoneal and mediastinal lymph nodes in young males	Germ cell tumour protocols
Metastatic squamous cell carcinoma in high cervical lymph node	Radical head and neck cancer protocols
	Mucositis
	Hand-foot syndrome

Table 3: Subgroups of patients with CUP associated with improved survival.

Molecular analysis techniques, such as the commercial gene expression profiling test (CupPrint®), may have a role in identifying the location of the primary tumour in patients with CUP, to help guide appropriate chemotherapy treatment. The test allows the analysis of a tumour specimen using a micro array (a single slide with 8 sub-arrays each containing 1,900 probes), which measures the activity of 500 cancer-type specific genes. The genomic profile of the tumour specimen is compared with a database of genomic profiles of 49 different tumour types. A 5 nearest neighbour algorithm is used to determine the five most molecularly similar tumours in the CupPrint® database. Diagnostic algorithms, such as this, have been shown to be able to correctly identify the primary sites of known primaries in 88% of cases[3] they are not yet used routinely in clinical practice. Immunohistochemistry, as an adjunct to conventional clinical and pathological investigations, remains the current standard of care in patients with CUP[1] although the success rate in identifying the primary with this technique is only 20%[7].

Management of the Patient

As in the case discussed above, patients often present with symptoms of undiagnosed metastatic cancer to A&E or acute medical and surgical assessment units. They may present with a variety of symptoms, such as weight loss, lethargy, nausea and vomiting, jaundice, bone pain, abdominal pain, abdominal distention due to ascites, breathlessness due to lung metastases or pleural effusions, headaches and neurological symptoms and acute renal failure. Patients may also present with oncological emergencies, such as spinal cord compression, hypercalcaemia, superior vena cava obstruction and hyperkalaemia, which require urgent investigation and treatment as per local hospital guidelines.

The management of patients presenting with symptoms of metastatic cancer should initially comprise of a thorough history and examination. Physical examination should include a thorough head and neck, thyroid examination, pelvic and rectal examination, examination of lymph node areas, breast examination in females and testicular examination in males. Features, such as a chronic cough or rectal bleeding or the finding of a pleural effusion or hepatomegaly, may help to guide subsequent investigations.

Blood tests should include FBC, U&E, LFT, bone profile and a clotting screen. Tumour markers, such as CEA, CA19–9, CA15–3 and CA125, may provide useful additional guidance as to the location of the primary tumour but should not be routinely requested (see Table 4). In cases of adenocarcinoma in male patients, immunohistochemical analysis should include PSA staining to assess for a prostate primary. Likewise ER and PR receptors should be tested in women with adenocarcinoma to assess for a breast primary.

Tumour marker	Primary tumour site
CEA	Colon cancer
CA19–9	Pancreatic cancer (also elevated in gastric and oesophageal cancer and in the presence of liver MetS and ascites)
CA 15–3	Breast cancer
CA125	Ovarian cancer
AFP and beta-hCG	Non-seminomatous germ cell tumours
PSA	Prostate cancer

Table 4: The association of tumour markers with primary tumour site.

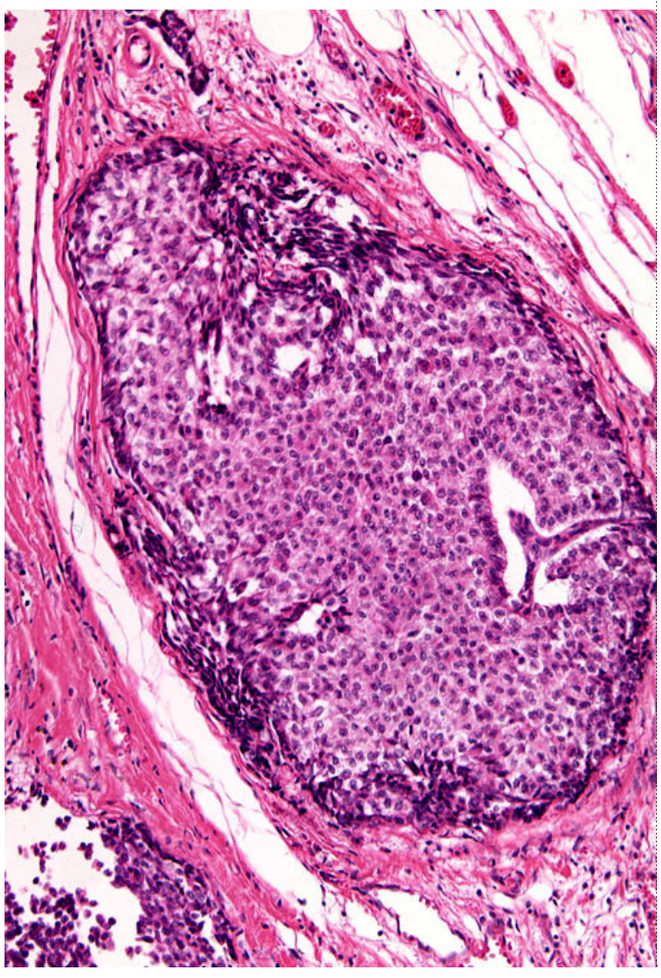
METASTATIC CARCINOMA OF UNKNOWN PRIMARY- CASE BASED DISCUSSION

Daniel Krell

Appropriate imaging investigations should be organised, to locate the primary tumour and to find a site amenable to biopsy. A CT scan of the chest abdomen and pelvis is required. In cases of adenocarcinoma in female patients, a mammogram should be performed. Other investigations may include chest X-ray, abdominal US, OGD, colonoscopy, ERCP and urinalysis. If spinal cord compression is suspected, an urgent MRI spine is required.

Patients should be referred early to the relevant oncology multidisciplinary team (MDT) meeting. The MDT will advise on appropriate further investigations and decide how to obtain a histological diagnosis. The MDT should be provided with information pertaining to the patients co-morbidities and performance status, as it may be inappropriate to expose the patient to serial investigations if they would not tolerate oncological treatment. Once a diagnosis of CUP is made, the MDT will facilitate referral to the appropriate oncological service.

The oncologist will either see the patient on the ward or urgently in an outpatients clinic. Prior to discharge, it is important to ensure that the patient is referred to the community Macmillan or palliative care services and is provided with contact details of their clinical nurse specialist.



Breaking bad news

The patient should be given the diagnosis of cancer by the admitting team prior to being seen by the oncologist. The doctor should be accompanied by the patients named nurse or clinical nurse specialist. The patient should be given the opportunity to have a relative present and privacy should be maintained. Assess the patients perception of their condition and warn the patient that bad news is coming before proceeding. Provide information slowly and in a comprehensible manner. Encourage the patient to ask questions and give them time to do so. Provide a clear plan for the future and explain that you have referred the patient to an oncologist, who will arrange to see them urgently. At the end of the discussion provide the patient with contact details of support organisations (e.g. Macmillan services) and offer to return later to discuss things further, and to speak to other family members if the patient wishes. Finally document the discussion clearly in the notes.

Multiple choice questions

1. Metastatic adenocarcinoma of unknown primary is associated with a median survival rate of:

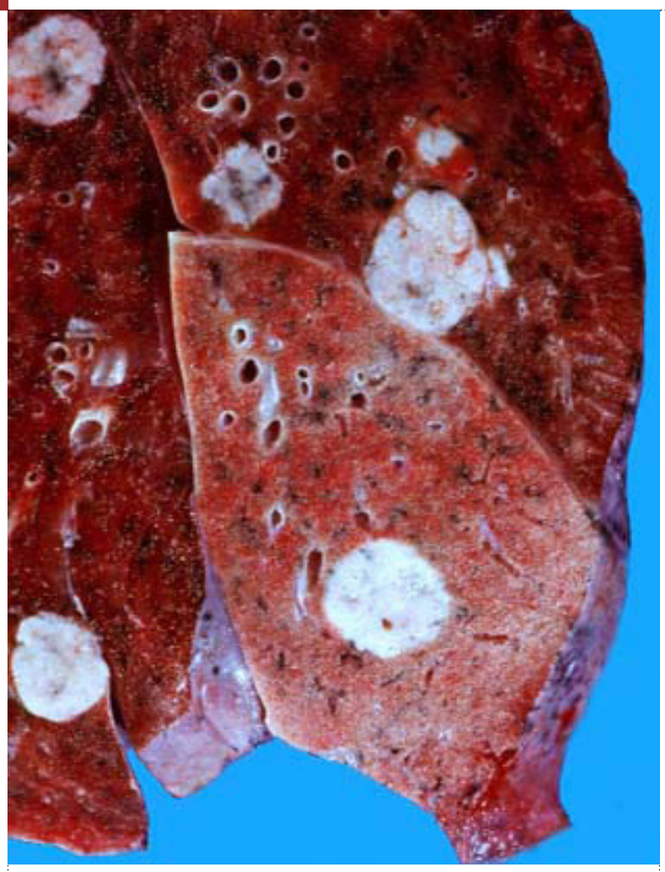
a. 3 months.
b. 8 months.
c. 12 months.
d. 18 months.
e. 24 months.

2. Regarding the WHO performance status scale, used to assess a patients fitness for chemotherapy, an performance status of 2 indicates that the patient is:

a. Asymptomatic.
b. Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
c. Symptomatic but completely ambulatory.
d. Bedbound and cannot carry on any self-care.
e. Symptomatic and capable of only limited self-care. Confined to bed or chair 50% or more of waking hours.

METASTATIC CARCINOMA OF UNKNOWN PRIMARY- CASE BASED DISCUSSION

Daniel Krell



Answers

1. b. 8 months.

CUP is associated with a median survival of 6–8 months. This is poor and significantly less than the expected survival for patients with a confirmed primary, following standard therapy. CUP is generally treated with platinum/taxane-based combination chemotherapy, although cisplatin/gemcitabine combinations have also been shown to be effective. Response rates are, however, disappointing (20–30%) and treatment should be considered palliative. There are, however, subgroups of patients who present with CUP that may be treated with tumour-specific chemotherapy, with an expectation of a significantly improved survival or in some cases cure. Unfortunately these subgroups represent only 5–10% of cases.

2. b.

Symptomatic, ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours (see Table 1).

The WHO performance status scale is used in oncology to quantify a cancer patient's general well-being. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary and as a measure for the required intensity of palliative care. It is also used in oncological randomised control trials as a quality of life assessment tool.

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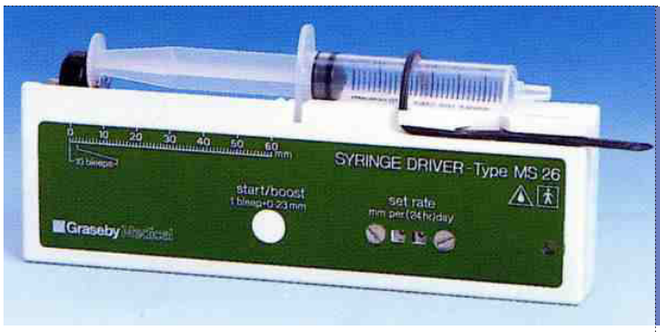
THE SYRINGE DRIVER: INSTRUCTIONS FOR USE AND POTENTIAL PITFALLS

Amy Gadoud and Fiona Hicks



The syringe driver.
Practical Procedures.

Abstract

The syringe driver is an excellent aid to symptom management for palliative care patients who would benefit from drugs delivered by continuous subcutaneous infusion (CSCI). It can be used in many situations including short-term control of nausea and vomiting or providing medication to patients who cannot swallow in the last days of life. As with any medical intervention, it is important to be clear about its purpose and not to use it unnecessarily. If the oral route for medications is appropriate it is preferred and it is important to remember that not all dying patients will need a syringe driver. In common with other medical devices, there is the potential for making mistakes in setting up syringe drivers and it is important for doctors to be familiar with the differences between the models available and their settings, in addition to the practicalities of setting up and using the equipment.

This article describes when to consider prescribing drugs by CSCI via a syringe driver, how to avoid errors in prescribing and initiating the infusion, dose conversions and common examples of drugs that can be mixed in the syringe.

Introduction

This article outlines what a Foundation doctor needs to know about using syringe drivers for their patients. It concentrates on the use of syringe drivers to administer continuous subcutaneous infusions (CSCI) of medications in the palliative care setting. Initially it will define what a syringe driver is and the advantages and disadvantages of giving medication this way. The main part of the article will focus on when and how to prescribe medication to be given this way.

What is a syringe driver?

A syringe driver is a portable, battery-operated device designed to administer a constant amount of a medication, usually subcutaneously. It is commonly used in palliative care but has a role in other settings. For example, they were initially devised to administer infusions of desferrioxamine to patients with thalassaemia[1].

Indications

If the oral route for medication is available it is always preferable. Except in the case of poor absorption of oral drugs, pain that is not responsive to oral morphine will similarly not respond to parenteral diamorphine or morphine given at an equivalent dose. This is a common error, and as the Palliative Care Formulary describes more succinctly, the use of a syringe driver is not the fourth step of the World Health Organisation (WHO) analgesic ladder![2]

It is important to emphasise that CSCI via a syringe driver can be used in a variety of situations in palliative care and does not necessarily imply that death is imminent[3]. Short-term use to gain control of difficult nausea and vomiting before converting back to oral medication is common practice, for example.

Possible indications for a syringe driver include:

- Uncontrolled nausea and or vomiting.
- Bowel obstruction.
- Poor gastrointestinal absorption of drugs (e.g. a high output ileostomy).
- Swallowing difficulties.
- Unacceptable number of oral medications or volumes of syrups.
- Patient is unconscious or too weak to take oral drugs.

Advantages

When the oral route cannot be used in palliative care we consider three main routes. Some drugs are available as suppositories, although this is not always acceptable to the patient. Analgesics can be delivered for stable pain via the transdermal route, but subcutaneous administration may be more flexible if analgesic requirements are unstable or still being determined, or if several symptoms need managing concurrently.

The main advantage of a syringe driver is to allow continuous administration of a drug or combination of drugs, without the peaks, troughs and discomfort associated with multiple injections. It is less intrusive and uncomfortable than repeated injections, especially in cachexic patients[4]. There is reduced reliance on trained staff to give repeated injections, which is particularly useful in the community setting. There is some loss of flexibility with a CSCI as the dose is usually changed every 24 hours and so some extra injections or prn ("pro re natal" - as required medication) by other routes, such as suppositories, may still be needed[5].

THE SYRINGE DRIVER: INSTRUCTIONS FOR USE AND POTENTIAL PITFALLS

Amy Gadoud and Fiona Hicks

Portable syringe drivers are battery operated, generally lightweight and can be carried in a small bag or holder, which is convenient for mobile patients. As a small volume is given the medication is absorbed very quickly so there is little discomfort from tissue stretching[5]. Box 1 outlines the main advantages and disadvantages of using a syringe driver compared with repeated injections.

Advantages and disadvantages of CSCI via a syringe driver compared with other parenteral methods in a patient who can not take oral medications

Advantages
- Less need for repeated injections
- Round the clock comfort because plasma concentrations are maintained
- Control of multiple symptoms with a combination of drugs
- Portable therefore independence and mobility maintained
- Generally need to be loaded only once every 24 hours

Disadvantages
- Training necessary for staff to use the equipment
- Possible pain and inflammation at the infusion site
- Lack of flexibility if doses need frequent changes
- Lack of reliable compatibility data for some mixtures of drugs

Box 1: Advantages and disadvantages of CSCI via a syringe driver compared with other parenteral methods in a patient who can not take oral medications[2].

Prescribing medication to be given as a CSCI via a syringe driver

The usual rules of good prescribing apply when prescribing medication to be administered via a syringe driver. It should be a clear, legible prescription with the prescriber's contact details in case of queries. Controlled drug doses should be written in words as well as figures[6].

There should be a designated chart on which to prescribe the CSCI medication. Make it clear on the main drug chart that a separate chart is being used. Prescribe the drug dose in milligrams or micrograms per 24 hours and include the diluent which is often water for injection.

For example, Cyclizine 150mg mixed with water for injection to be given via continuous subcutaneous injection over 24 hours via a syringe driver.

Many drugs that are commonly given by the subcutaneous route are not licensed to be given by this route or to be combined in a syringe. In palliative care, drugs are often given outside their product licence. A statement from the Association for Palliative Medicine and the British Pain Society supports the use of drugs "off licence" and provides guidance for prescribers[7].

For converting from oral medication, see examples given in "Using the syringe driver in the dying patient" section below. Many drugs undergo first pass metabolism when given orally and the dose must therefore be reduced for subcutaneous use. If you are in any doubt, you should consult the BNF or check with a senior medical colleague, pharmacist or palliative care specialist.

It is essential to ensure that appropriate prn medication is prescribed. For opioids this is usually one-sixth of the 24-hour dose. When first starting a CSCI, consider giving a single dose of prn medication as it takes a few hours for the infusion to reach a therapeutic dose.

An advantage of the giving drugs by CSCI, via a syringe driver, is that more than one drug can be given in the same syringe. This is convenient for the patient and allows multiple symptoms to be controlled. However, not all drugs are compatible. It is therefore, advisable to check before mixing drugs especially if using more than two drugs. Table 1 demonstrates some common two drug compatibilities.

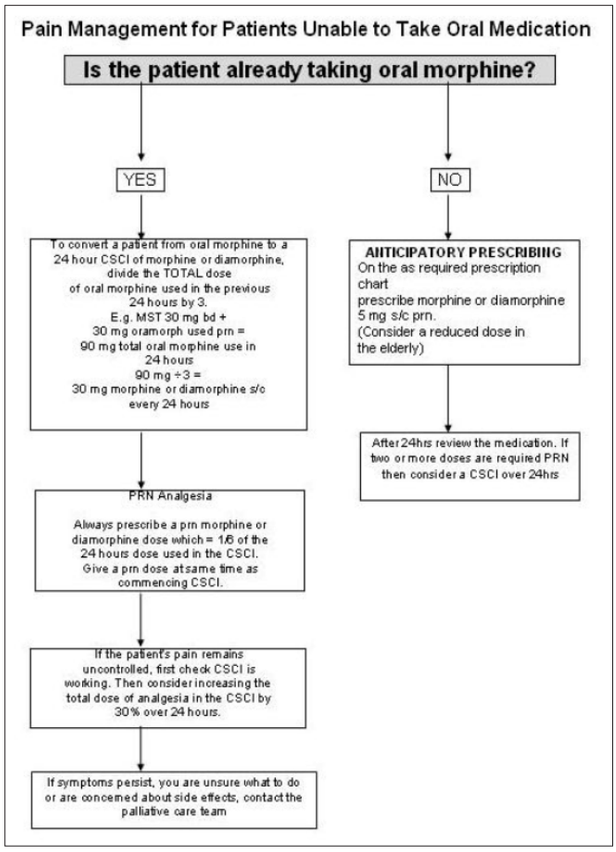


Figure 1: Pain Management for patients unable to take oral medication[11].

THE SYRINGE DRIVER: INSTRUCTIONS FOR USE AND POTENTIAL PITFALLS

Amy Gadoud and Fiona Hicks

Using the syringe driver on the dying patient

An important use of a syringe driver is to aid symptom control for a dying patient who is too frail to swallow. Care of the dying is a core skill for all doctors[9] and all Foundation doctors should be able to prescribe appropriate drugs in this situation. The Liverpool Care Pathway (LCP) is a useful document to assist with this. The LCP appendix includes prescribing guidelines for the common symptoms of pain, nausea and vomiting, respiratory tract secretions, and terminal restlessness and agitation[10]. Figure 1 shows an example of a flow chart for guidance on what to prescribe for pain. It is essential to ensure that prn subcutaneous medication for these symptoms is prescribed.

Drug Compatibility Chart	Diamorphine*	Morphine sulphate	Cyclizine *	Metoclopramide	Haloperidol	Levomepromazine	Hyoscine Hydrobromide	Hyoscine butylbromide*	Midazolam	Octreotide	Glycopyrronium
Diamorphine *			C	C	C	C	C	C	C	C	C
Morphine sulphate			C	C	C	C	C	C	C	C	C
Cyclizine*	C	C		X	C	X	C	C	C	N	N
Metoclopramide	C	C	X		X	X	X	X	C	C	N
Haloperidol	C	C	C	X		X	N	C	C	N	N
Levomepromazine	C	C	X	X	X		C	C	C	C	C
Hyoscine Hydrobromide	C	C	C	X	N	C		X	C	X	X
Hyoscine butylbromide *	C	C	C	X	C	C	X		C	C	X
Midazolam	C	C	C	C	C	C	C	C		C	C
Octreotide	C	C	N	C	N	C	X	C	C		N
Glycopyrronium *	C	C	N	N	N	C	X	X	C	N	

C Compatible at usual concentrations. Check with Pharmacy or PCT first if unsure.

X Combination not suitable and / or not appropriate due to antagonism or overlap in effect. Check with Pharmacy or PCT.

N Little or no information available. Check with pharmacy or PCT

Table 1: Compatibility of two drugs in a syringe driver[11].

*Concentration dependent compatibility problems can occur with combinations of cyclizine and diamorphine, cyclizine and hyoscine butylbromide, cyclizine and glycopyrronium. Seek advice for further information. The standard diluent for any of the drugs listed above is water for injection. (Palliative Care Team). Reproduced by permission from Ankrett H, Alison D, Bagley J et al. Guidelines for the use of the MS 16A Graseby syringe driver for continuous subcutaneous infusion in the symptom management of adult patients. Available from Leeds Teaching Hospitals' NHS Trust, May 2007. Adapted from Dickman A, Schneider J and Varga J. The syringe driver: continuous subcutaneous infusions in palliative care.[8]

The main indications for using a syringe driver for administering medication to a dying patient are:

- Uncontrolled symptoms or symptoms that have required more than two doses of the prn medication.
- If symptoms have been well controlled on oral medication (e.g. pain with opioids) and the patient is now unable to swallow, it is necessary to convert the medication to an equivalent dose via a CSCI.

For example, a patient, previously well pain controlled on morphine sulphate MR 30mg bd is now dying and is too weak to swallow. To determine the 24-hour dose of morphine by CSCI, it is necessary to divide the daily dose of oral morphine by 3. In this example 60mg is divided by 3 giving a dose of morphine 20mg subcutaneously over 24 hours via syringe driver.

Some hospitals may use diamorphine or other opioids as the first line in place of morphine. The bioavailability of oral morphine varies substantially between patients so these conversions are safe approximations. Please check local guidelines as they may vary between units.

For anti-emetics the subcutaneous dose is generally the same as the oral dose but it is important to check that the anti-emetic can be given safely subcutaneously as some (e.g. prochlorperazine) are irritant.

If a patient is well symptom controlled using other routes of administration and these can be maintained in the dying phase, or the patient does not have symptoms, a syringe driver does not have to be set up routinely for terminal care.

THE SYRINGE DRIVER: INSTRUCTIONS FOR USE AND POTENTIAL PITFALLS

Amy Gadoud and Fiona Hicks

Fentanyl patches and the dying patient

If a patient has good analgesia from a transdermal fentanyl patch, there is no need to alter this in the dying phase. In case pain increases, it is good practice to prescribe an appropriate additional subcutaneous opioid as required. If more than two additional doses are needed in 24 hours, this may be given by CSCI, via a syringe driver, starting with a dose equivalent to the total additional dose of opioid used. In that period the fentanyl patch should be continued and changed every 72 hours as usual. This avoids a complex changeover period which risks loss of pain control or overdosage, as fentanyl takes 12–24 hours to increase or decrease on addition or removal of a patch. Remember to adjust the prn opioid dose taking into account the total daily dose (i.e. transdermal fentanyl and subcutaneous opioid)[12].

Guidance on when to start the syringe driver

When it has been decided to deliver drugs by CSCI in place of the oral route, it can be difficult to know when to start the infusion in relation to the last dose of the patient's usual medication. If a patient requires a syringe driver containing an opioid then when to start depends on what opioid they have been taking.

- Patient not currently on an opioid, just on prn opioid or regular immediate release opioid (e.g. oramorph) start as soon as practical.
- Patient on modified release opioid (e.g. MST) ideally should start when the last dose of modified drug would have been due.
- If the patient's pain is not well controlled, give a prn dose of opioid at the same time as starting the syringe driver. This should be approximately a sixth of the 24-hours dose.
- If the syringe driver is started when the patient's pain is well controlled then a loading dose of opioid is not necessary.

Types of syringe drivers

There are four main models of syringe driver in use and it is important to familiarise yourself with your local model, policy and prescribing guidelines.

- The most widely used models currently are the Graseby® MS26 green (rate mm per 24 hours) and the Graseby® MS16A blue (rate mm per hour). Note that with the Graseby® syringe drivers the rate of delivery is determined by length of the infusion fluid rather than volume of the syringe. Significant errors can occur if two types of syringe driver are confused as their rates are very different. In addition the MS26 model has a boost button which is best ignored. The amount of analgesia administered is much less than the recommended one-sixth dose and if other drugs are mixed in the syringe they will be given at the same time. There is no lock out period so if the button is pressed persistently, it could lead to overdose.

- The McKinley® T34 and Alaris® AD syringe drivers are newer models that can be programmed to infuse in ml/hr and have other safety features[13]. It is likely that these will become more widely used.

Setting up a syringe driver

Trained nursing staff will set up the syringe driver according to your prescription. As with all medical devices they should only be set up by someone who has been trained to use them. In hospital it is recommended that they are checked every 4 hours by the trained nurse, ensuring that they are running to time, and checking for development of skin reactions and crystallisation or precipitation of the drugs in the syringe[13]. If you encounter any difficulty speak to more senior staff or the palliative care team for advice.

Where to site the injection

The trained nurse setting up the syringe driver will do this. Use an area of healthy skin with as much subcutaneous tissue as possible. The patient may express a preference.

- Anterior chest, anterolateral aspect of upper arm, anterior abdominal wall, anterior surface of thighs or upper back.
- Avoid oedematous areas, broken, inflamed or infected skin, bony prominences or previously irradiated skin[2].

Explanation to patient and/or relatives

There is a perception among the general public that if a patient has a syringe driver then they must be near to death or even that the syringe driver may hasten death[10]. It is therefore important to explain the reason for the syringe driver and explore their concerns and expectations. Explanation and education, for example, not to use the boost button, are also important. Written information may be helpful and may be available in your unit.

Infusion site problems

Local skin reactions at the needle site are commonly seen. There are many suggested causes and solutions for these. In general you should dilute the solution as much as possible and rotate the sites of infusion. Non-metal cannulae may need to be used. If problems persist, consider changing the drug combination[3]. You may need to involve senior colleagues or the palliative care team in this.

Reviewing the need for a syringe driver

The medical team should review the prescription for the CSCI, via a syringe driver, every 24 hours or earlier if there are any concerns. The side effects and effectiveness of the medication should be reviewed and any changes initiated.

The reason for using a syringe driver should be regularly reviewed. For example, if it was started for nausea and vomiting and the symptoms have settled or the cause corrected, it would be reasonable to convert to oral medications or even stop the anti-emetic. Similarly once pain has stabilised and the oral route is not possible conversion to a transdermal opioid patch may be more convenient.

THE SYRINGE DRIVER: INSTRUCTIONS FOR USE AND POTENTIAL PITFALLS

Amy Gadoud and Fiona Hicks

Discharging a patient who is on a syringe driver

A patient can be discharged home, to a hospice or to most nursing homes with a syringe driver in place. It is important to ensure that you prescribe a supply of all medication and the diluents (e.g. water for injection) on "the medicines to take home form". Patients will also need a supply of prn medication in a suitable form and know how to take it or who to contact to give it. The district nurses will need to be contacted to ensure that they come in daily to reload the syringe driver. The time of changing the syringe driver may need to be changed in hospital to be a convenient time for the patient and district nurse to change at home. There will be a local policy on loaning the syringe driver to the community team and how it should be returned. In order to deliver the medication at home, the district nurse will need a community prescription to be written. This is usually done by the GP but does depend on local arrangements. It is important to notify the GP as soon as possible about the patient's discharge and to provide timely information to allow good continuity of care. Taking time to address any patient and/or family concerns prior to discharge and giving them clear instructions about who to contact if they have any problems is also very helpful.

Internet resources

- **www.cancernursing.org:** free e-learning package on Graseby syringe drivers in palliative care, especially how to set them up.
- **www.pallcare.info:** information on syringe driver drug compatibility.

Conclusion

In an article like this it is necessary to focus on the potential pitfalls, but I would like to end on a personal note. The syringe driver is an excellent tool in symptom management. When correctly used, it is immensely satisfying to control what might have been very troublesome symptoms with this simple device.

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MANAGEMENT OF THE FEBRILE NEUTROPAENIC PATIENT

James A. Richards

Mrs S is a 44-year-old lady who has been brought in by ambulance to the A&E of her local district general hospital, accompanied by her husband.
Patient Management.

Mrs S is a 44-year-old lady who has been brought in by ambulance to the A&E of her local district general hospital, accompanied by her husband. He contacted their GP when she began feeling unwell early that morning, with rigors and a temperature of 39ºC (recorded at home); her GP advised that she come directly to hospital. She is on a long course of chemotherapy for acute myeloid leukaemia (AML) and was discharged from hospital 1 week ago. On arrival in the A&E, Mrs S is flushed and looks unwell. Her initial observations are as follows: pulse 98 beats per minute; BP 95/60; respiratory rate 24; oxygen saturations 95%; and temperature 38.5ºC. A urine dipstick revealed a trace of protein and ketones+, but no nitrites or leucocytes. Chest X-ray is unremarkable, other than Mrs S's Hickman line in her right subclavian vein. She is commenced on intravenous fluids and given paracetamol for her temperature.

You are the FY1 doctor on-call and you are asked to clerk the patient for admission, prior to assessment by the haematology SpR, who is on-call from home; and will be in the hospital in around 45 minutes.

What are the key elements of the history?

The purposes of taking a history in a patient who may be neutropaenic are threefold: first, following appropriate initial resuscitation, it is essential to consider the fact that a patient who is undergoing or has undergone chemotherapy (or has a haematological or oncological condition) is at risk of neutropaenia and is subsequently at increased risk of severe and rapidly progressive infections. Second, it is important to enquire as to the duration of the symptoms and how rapidly these have progressed. Third, a systematic review of the possible sources of the infection is needed; this can be considered by each organ system: the brain and meninges, any headache, neck stiffness, photophobia or rash; the respiratory system, with a productive cough or shortness of breath; the heart, considering any recent dental procedures, the presence of mechanical heart valves and other risk factors for infective endocarditis; the abdomen, considering the presence of abdominal pain or diarrhoea, rectal pain or discomfort; the urinary tract, dysuria and urinary frequency; and the skin, any redness or swelling signalling cellulitis. It is also important to consider potential iatrogenic sources of infection, such as indwelling venous catheters (e.g. Hickman lines), which are often used on a long-term basis in patients receiving chemotherapy and blood products[1].

You ask Mrs S to describe exactly what has happened, in her own words. She says that she was discharged from hospital 1 week ago and the doctors were a little reluctant to send her home as her white blood cell count had only just recovered, but she was very keen to get back home to spend some time with her children and husband. She was feeling a little tired, but otherwise well until this morning when she could feel that she had developed a high temperature and began shivering violently. She remembered that she was feeling well the previous day as the district nurse, who comes in to check on her and assess her Hickman line site, had visited. Her husband was very concerned when he was woken by her shivering. She has no dysuria nor urinary frequency and no cough or sputum production. She describes no other localising symptoms of infection, although the district nurse had commented that the area of skin around her Hickman line was a little red and she was going to see the doctors in the drop-in clinic in 2-days time.

Mrs S has had two previous serious infections when she was neutropaenic during the treatment for her AML and she had felt similar to this, with high temperatures and violent shivering. On one occasion she had to be looked after on the high dependency unit, as she needed treatment for her low blood pressure. She is very concerned about this.

Mrs S's past medical history includes: gallstones, for which she had a cholecystectomy in 1998; a course of in-vitro fertilisation; and an episode of reactive depression, which occurred 2 months after her initial diagnosis with AML.

Her medications include acyclovir 400mg od, chlorhexidine mouthwash, which she uses four times a day and fluoxetine 40mg od. She has no known drug allergies.

She lives with her husband and her two children, both girls, aged 9 and 11 years. Her husband is a great support, but has struggled with working while looking after their two daughters and travelling to visit her during her long inpatient stay. Their children are currently at home being looked after by their grandmother.

MANAGEMENT OF THE FEBRILE NEUTROPAENIC PATIENT

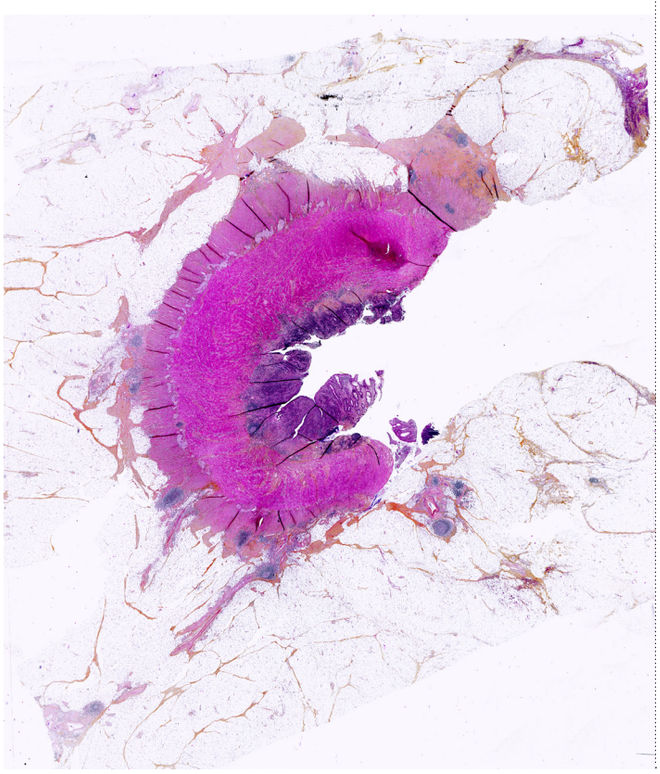
James A. Richards

What are the causes of and risk factors for neutropaenia?

Neutropaenia is defined as a neutrophil count of less than 1.5 x 10^9/L and the risk of infection increases as the count falls, being highest at neutrophil counts of less than 0.5 x 10^9/L^2. There are many different causes of neutropaenia; the most important and commonly encountered are secondary to haematological malignancies; including the acute leukaemias and forms of lymphoma; and that caused by the treatment of these conditions with chemotherapy. It is important to note that drugs that can cause neutropaenia are also commonly used in chemotherapy regimes for other forms of cancer (such as lung, breast and bowel cancers) and also as part of the treatment for autoimmune conditions (such as rheumatoid arthritis). Neutropaenia usually occurs 7 to 14 days after chemotherapy and so it is essential to consider this in any patient who presents after recently having undergone a course of chemotherapy. With some agents neutropaenia can occur later, but this is rare.

In order to consider the causes of neutropaenia, it is important to understand the origin of the cells of the blood. Neutrophils are produced from stem cells within the bone marrow, which also give rise to all other components of blood (red blood cells, lymphocytes, eosinophils and so on); they mature here and are then released into the circulation. They combat infections, both at local sites (such as a wound in the skin) and also within lymph nodes. Neutrophils are the immune system's first cellular line of defence against infection.

The causes of neutropaenia can be divided into those in which production of neutrophils is reduced, in which neutrophils are broken down too rapidly and in which they are used up too quickly.



The common causes of neutropaenia are summarised below:

Cause of neutropaenia	Examples
Reduced production of neutrophils	**Congenital disorders:** these tend to present in infancy and early childhood (e.g. Kostmann syndrome) **Bone marrow infiltration:** acute and chronic leukaemias Lymphoma (Hodgkin's disease and non-Hodgkin's lymphoma) Metastatic spread of carcinoma (including prostate and lung cancer) **Stem cell suppression:** chemotherapy agents, causing dose-related damage to the bone marrow stem cells (these may also cause anaemia and thrombocytopaenia – pancytopaenia)
Increased destruction of neutrophils	**Drug-related causes:** (e.g. carbimazole, penicillins, phenytoin) **Autoimmune neutropaenia:** this may be associated with rheumatoid arthritis or systemic lupus erythematosis
Increased consumption of neutrophils	**Sepsis:** in severe infections, the body's stores and capacity for production of these cells are overwhelmed

What is the significance of an infection in a neutropaenic patient?

Why is it important to consider neutropaenia in patients presenting with symptoms and signs of an infective process who have recently completed a course of chemotherapy? How is this different from any other patient presenting with an infection?

MANAGEMENT OF THE FEBRILE NEUTROPAENIC PATIENT

James A. Richards

The immune system is remarkably effective in fighting off infections in the immunocompetent person. Everyone is exposed to a huge number of infectious microorganisms every day, but the immune system rapidly controls potential infections, preventing spread into the blood stream, bacteraemia and sepsis. However, in neutropaenic patients, the body's first cellular line of defence is depleted, allowing infections that would not usually be clinically apparent to progress rapidly. In patients with a significant neutropaenia, an infection can progress to sepsis, with dissemination of the bacteria throughout the bloodstream, leading to multi-organ failure and even death within hours to days. Thus early recognition, assessment and treatment of neutropaenic sepsis are essential[3].

Although much of the treatment of neutropaenic sepsis is undertaken by haematologists, patients with febrile neutropaenia often present on the general medical take and particularly because the initial management is so important in preventing progression, it is essential that the FY1 doctor is familiar with the treatment and potential complications of this condition.

What are the particular points to note during your clinical examination?

The initial assessment of a patient with febrile neutropaenia, as with all acutely unwell patients, incorporates assessment of the airway, breathing, circulation and neurological disability. With respect to neutropaenic sepsis, the blood pressure, pulse and temperature are particularly important, as in severe sepsis the blood pressure can be compromised. In a hypotensive, tachycardic patient whose blood pressure does not improve with an intravenous fluid challenge, a senior member of staff (ST1 to consultant grade) should be involved immediately to assess the need for circulatory support on the high dependency or intensive care unit.

Following initial resuscitation, a through examination is essential to locate the source of infection and to look for potential complications associated with sepsis. Examination of the respiratory, cardiovascular and abdominal systems may reveal a potential source of infection. Do not forget to assess the perianal area. Assessment of the neurological system may reveal neck stiffness or photophobia. A survey of each joint may reveal a previously unnoticed septic arthritis. However, in neutropaenic sepsis often there are no localising signs, merely a systemic inflammatory response.

A systemic inflammatory response syndrome is defined as two or more of:

- heart rate >90 beats per minute
- temperature <36°C or >38°C
- respiratory rate >20/minute
- white cell count <4 x 10^9/L or >12 x 10^9L.

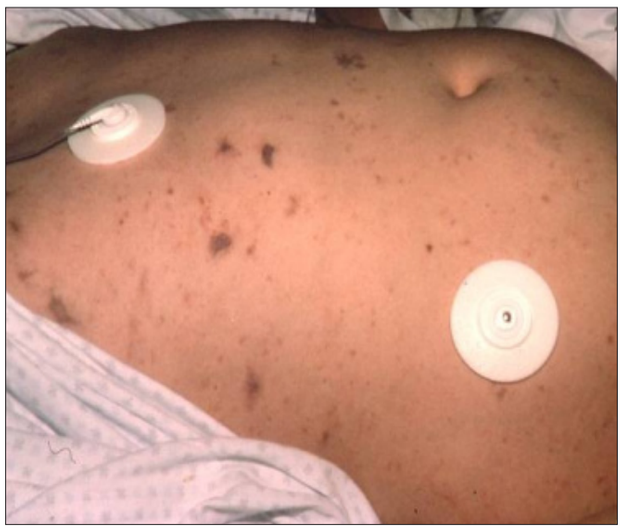
Sepsis is defined as a combination of signs of an infective process together with a systemic inflammatory response syndrome[4].

The relevant findings from Mrs S:

- Airway: patent.
- Breathing: respiratory rate 24. Oxygen saturations 95% on air.
- Circulation: BP 95/60. Pulse 98 BPM. Warm peripheries.
- Disability: Alert. Glasgow coma scale 15/15. BM 7.6.
- Temperature 38.5°C. Looks flushed and unwell.
- Examination of the cardiovascular, respiratory, abdominal and neurological systems is normal.
- The neurological system is intact and there are no hot, swollen or tender joints. There are no skin rashes.
- Mrs S has a right-sided Hickman line (tunnelled central venous catheter). The site is inflamed with a 1cm rim of local redness.

In a patient with febrile neutropaenia, a number of complications can occur. These include acute renal failure which, although usually recognised through blood tests, could be signalled by an elevated respiratory rate. In severe acute renal failure and acidosis, there is compensation for this acidosis by an increase in the respiratory rate, which removes more carbon dioxide from the circulation and brings the pH towards normal (metabolic acidosis with respiratory compensation)[5].

One serious complication of sepsis (neutropaenic and otherwise) is disseminated intravascular coagulation (DIC). This can present with a purpuric, non-blanching rash on the skin, excessive bleeding from venesection sites and life-threatening haemorrhage[1].



DIC occurs as a response to severe infection: the blood's clotting system is excessively and inappropriately activated, causing initial microvascular thrombosis, depletion of the blood clotting mechanisms and subsequent tendency to life-threatening haemorrhage. It is essential to recognise this life-threatening complication and involve senior doctors, including the intensive care team and a haematologist.

MANAGEMENT OF THE FEBRILE NEUTROPAENIC PATIENT

James A. Richards

What baseline investigations should the FY1 initiate?

Important initial investigations include the following:

• **Blood tests:** a full blood count, to assess for neutropaenia, urea and electrolytes, glucose and liver function tests including albumin. A clotting screen should be performed, as a raised INR and a low fibrinogen, combined with thrombocytopaenia may signal DIC. A blood film will reveal red cell fragments in DIC. Erythrocyte sedimentation rate and C-reactive protein are useful in monitoring the course of the infection and response to treatment. An arterial blood gas may reveal an increased lactate.

• **Microbiology specimens:** blood cultures should always be taken, ideally before the administration of antibiotics, from both a peripheral site and any central venous catheters[3]. A mid-stream urine and swabs of any wounds.

• **Radiology:** chest X-ray may reveal signs of consolidation. Other investigations will be guided by the clinical presentation.

• **Others:** an ECG should be performed routinely in the acutely unwell patient.

Further management of Mrs S

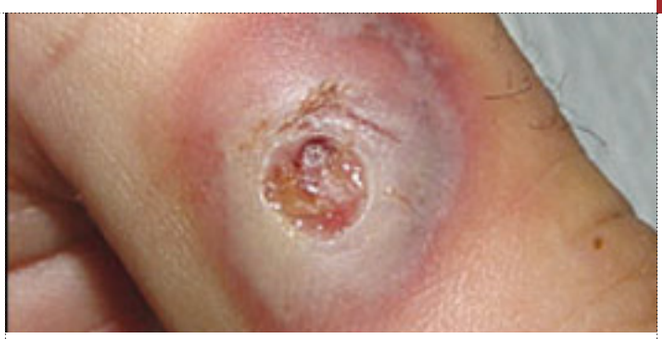
Mrs S improved rapidly with intravenous fluids and following 1L 0.9% saline her blood pressure rose to 110/70, her pulse falling to 84 BPM. After having blood cultures taken, she was given broad spectrum antibiotics within 1 hour of her admission to hospital. Mrs S's neutrophil count was 0.8 X 10^9/L and so she was continued on broad spectrum antibiotics according to the hospital's protocol for neutropaenic sepsis. Her urea and electrolyes were abnormal, with a urea of 14mmol/L and a creatinine of 160µmol/L, reflecting a combination of dehydration and sepsis. Intravenous fluids were continued for 48 hours.

The Haematology SpR recommended that Mrs S be managed on a haematology ward in a side room, with reverse barrier nursing. Blood cultures grew group A *streptococcus,* which was felt to have originated from a locally infected Hickman line. This was removed the following day. She made excellent progress and was discharged home on oral antibiotics 5 days later. At this time her neutrophil count had recovered to 3.2 X 10^9/L.

How can we improve the treatment of patients with febrile neutropaenia?

First, it is essential to have a high index of suspicion for infections in patients who are or may be neutropaenic. Infections in these cases are a medical emergency, as they can progress rapidly. Senior medical staff, including haematologists and intensive care teams, should be involved at an early stage.

In 2004, the Society of Critical Care Medicine commissioned the *Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock*[3]. These guidelines were produced by experts in the fields of medicine, intensive care and microbiology, among others; the aim being to improve the treatment of patients with sepsis.



The Surviving Sepsis guidelines of relevance to the initial management of these patients, and therefore of importance to the FY1 doctor, are as follows:

• Early, rapid initial resuscitation is of paramount importance. If the patient is not responding to these measures, admission to the high dependency or intensive care unit will be required.

• Blood cultures should be taken before the administration of antibiotics. These will guide future antimicrobial treatment and also give an indication as to the source of infection.

• Broad spectrum antibiotics should be given within 1 hour of the recognition of sepsis. This reduces the likelihood of progression to multi-organ failure and death.

• In severe sepsis, the source of infection (such as an intra-abdominal collection or an infected Hickman line) should be removed as soon as is possible.

• Consideration should be given to stress ulcer prophylaxis (with a proton-pump inhibitor or H2-antagonist) and to deep vein thrombosis prevention, with TED stockings and low-molecular weight heparin, as long as these are not contraindicated.

Although patients with febrile neutropaenia are often managed by haematologists, it is essential that the FY1 doctor is familiar with the treatment of this patient group, as early, goal-directed treatment saves lives.

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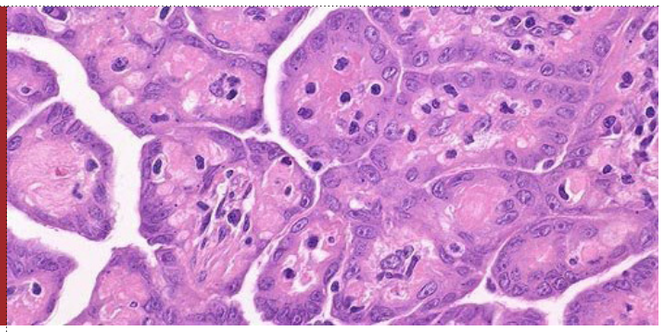
CASE BASED DISCUSSION: MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Burhan Khan and Majid Mushtaq

Malignant pleural mesothelioma (MPM) is an uncommon cancer that has become a very important public health issue due to its increasing incidence worldwide as a result of widespread exposure to asbestos. Patient Management.



Abstract

Malignant pleural mesothelioma (MPM) is an uncommon cancer that has become a very important public health issue due to its increasing incidence worldwide as a result of widespread exposure to asbestos. This is set to increase for at least the next 10 years. Occupational asbestos exposure has been clearly established as the main factor involved in MPM pathogenesis. However, the screening and diagnosis of MPM in asbestos-exposed subjects is difficult. First, the disease may occur up to 30–40 years after exposure and second, differentiating between MPM, benign pleural disease and pleural metastasis of adenocarcinoma on histology may be difficult in some cases, even with immunohistochemistry.

Usually a diagnosis of MPM carries a dismal prognosis with limited therapeutic options. Managing the troublesome symptoms of recurrent pleural effusion accumulation and wound seeding are key. Radiotherapy is used prophylactically to prevent the seeding of tumour cells in the chest tube tract or surgical wound sites, as well as for pain relief and local recurrence. However, there have been several recent developments in the management, including more accurate staging and patient selection; improvements in surgical techniques and postoperative care; novel chemotherapy regimens; and new radiotherapy techniques. When localised, it is amenable to curative resection, but MPM usually presents as a diffuse and advanced disease with poor survival. Chemotherapy remains the mainstay of treatment and now several newer anti-tumour agents and multimodality treatments have shown promising results in select cohorts of patients.

You are asked to see a 68-year-old man who presents to the A&E with a 6-weeks history of worsening shortness of breath, dry cough and accompanying pleuritic pain on the right side of the chest. He has no expectoration or haemoptysis, but has definitely lost weight. He has no significant past medical history and is not on any regular medicines. He has smoked 20 cigarettes per day since he was 18 years old, but stopped smoking 10 years ago.

How would you asses him?

Assess ABC (airway, breathing, circulation) first and stabilise the patient. If oxygen saturations are low he will require controlled supplementary oxygen, preferably via a venturi mask, titrated accordingly.

A thorough history including occupational history, allergies and exposure to allergens is essential. This should be followed by a thorough examination and investigations including arterial blood gases and a chest X-ray.

Further history reveals that he is a retired carpenter and has worked with asbestos, cutting asbestos boards but approximately 30 years ago. He has no allergies or pets.

Examination reveals saturations of 96% on room air with a respiratory rate of 18/min at rest. Chest excursion is asymmetrically reduced on the right with a stony dull percussion note and reduced breath sounds. Chest X-ray shows an opacification occupying two-thirds of the right hemithorax.

What would you do next?

The clinical examination and chest X-ray suggests that the patient has a large right-sided pleural effusion. The next step would be to do a diagnostic pleural thoracentesis. Ideally this should be done with ultrasound guidance, however, one careful attempt with a green needle is permitted. Macroscopic examination of the fluid should be noted. Common causes of haemorrhagic pleural effusion are trauma, traumatic tap, malignant mesothelioma and malignancies, pulmonary embolism and rarely tuberculosis. Samples should be sent for analysis of pH, protein, glucose, amylase, lactate dehydrogenase (LDH), gram staining, culture, acid-fast bacilli and cytology for cell count and atypical cells.

A therapeutic thoracentesis or chest drain insertion is indicated if the patient is in respiratory distress or for relief of symptoms. This can be done safely either by the Seldinger technique under ultrasound guidance or by inserting a wide bore chest drain by blunt dissection.

CASE BASED DISCUSSION: MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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What are the precautions of doing a diagnostic thoracentesis?

A diagnostic thoracentesis is performed when a pleural effusion of unknown cause is present. Relative contraindications include: a bleeding diathesis; anticoagulation therapy; too small a quantity of pleural fluid; and mechanical ventilation. Possible complications of a thoracentesis include: pneumothorax; pain at needle site insertion; bleeding (local, intrapleural or intra-abdominal); empyema; and spleen or liver puncture.

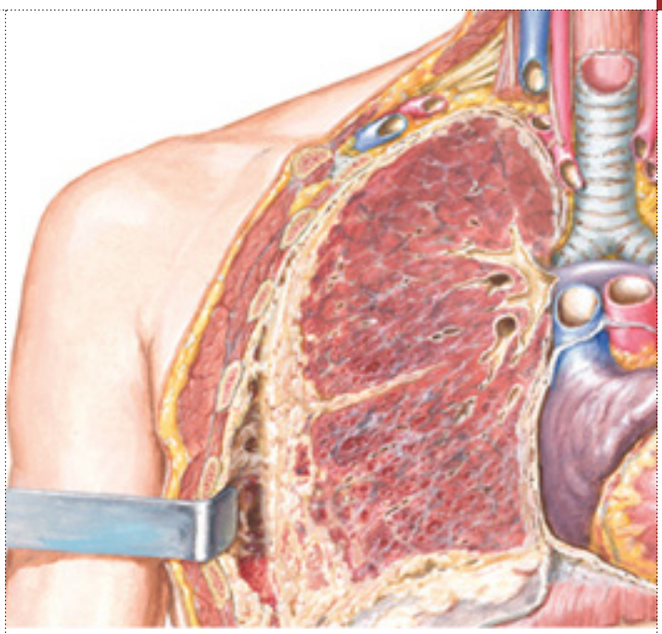
How would you interpret the results?

To differentiate between a transudate and an exudate, if any of the following criteria are present the fluid has a high likelihood of being an exudate: pleural fluid protein >29g/L; ratio of pleural fluid total protein to serum total protein greater than 0.5; ratio of pleural fluid LDH to serum LDH greater than 0.6; pleural fluid LDH >60% of the upper limit of normal serum LDH; and pleural fluid cholesterol greater than 45mg/dl (1.16mmol/L). Common causes of pleural effusions are listed in Table 1.

Transudates	Exudates
Congestive cardiac failure	Endometrial haemothorax
Constrictive pericarditis	Hypothyroidism
Duropleural fistula	Lymphoma/lymphoproliferative disorders
Extravascular migration of central venous catheter with saline effusion	Lung cancer
Hepatic hydrothorax	Metastatic malignant pleural effusion
Hypoalbuminaemia	Meigs' syndrome
Nephrotic syndrome	Malignant mesothelioma
Peritoneal dialysis	Pancreatic pleural effusion
Trapped lung	Parapneumonic pleural effusion
Urinothorax	Pulmonary embolism
	Rheumatoid pleuritis
	Tuberculosis
	Viral infections

Table 1: Causes of pleural effusion.

Though a pleural thoracentesis is often the first procedure to be carried out, a diagnosis of mesothelioma should not be based on cytology alone because of the high risk of error. Well differentiated malignant mesothelial cells are very difficult to distinguish from reactive mesothelial cells and sometimes may also have a pseudocarcinomatous aspect. Also, pleural cytology is completely inappropriate in sarcomatoid subtypes of MPM because they do not desquamate. Pleural effusion analysis usually shows a non-specific exudate with high levels of proteins, LDH and hyaluronic acid.



What investigation would help confirm the diagnosis of malignant pleural mesothelioma?

Chest high-resolution: CT scanning is a key imaging procedure and although not definitive, certain features, such as diffuse pleural thickening or mass with thickening of interlobular fissures, are highly suggestive of MPM. However, CT scans in patients with abundant pleural effusion often show non-specific features. Therefore, it is recommended that follow-up be carried out after removal of pleural fluid by a multi-detector CT scan with multi-planner reformation for diagnosis and staging of MPM.

Histopathology: diagnosis of mesothelioma from fine needle biopsies is associated with the same problems as cytology. A conclusive diagnosis can only be made if the material is representative of the tumour and in sufficient quantity to allow immunohistochemical characterisation. Sensitivity for the diagnosis of mesothelioma using fine needle biopsies is low (around 30%) and only goes up to 40% when using both pleural fluid analysis and transthoracic pleural biopsy. This may be improved further if the biopsies are guided by ultrasound or CT scan, but this is usually only possible at more advanced stages of disease. Thus, transparietal biopsies with or without CT scan, or ultrasound guidance, are not recommended for the diagnosis of MPM except in patients for whom thoracoscopy is contraindicated.

Thoracoscopy: medical thoracoscopy or video-assisted thoracoscopic surgery (VATS) are the optimal methods to confirm MPM when suspected. Diagnostic accuracy is greater than 90% and complications occur in less than 10% of cases. Advantages of thoracoscopy include high sensitivity and specificity; a better cost/efficiency ratio than surgery; and may also show tumour extension to the visceral pleura – a bad prognostic factor. It is also possible for therapeutic instillation of talc to achieve a pleurodesis in cases of recurrent pleural effusion and is being used in clinical trials to evaluate potential intrapleural anti-tumour treatments.

CASE BASED DISCUSSION: MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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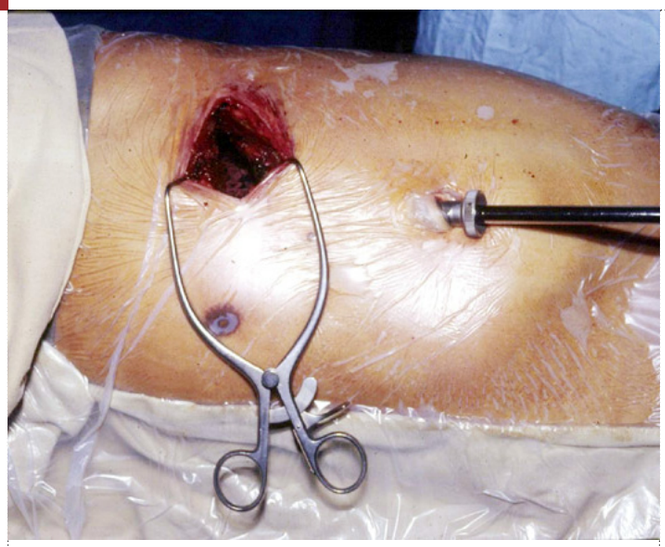

Mini-thoracotomy: direct access to the pleura enables tissue biopsies to be obtained for histological examination, notably in the absence of pleural effusion. However, this should be reserved for cases where thoracoscopy has failed.

Immunohistochemistry: the diagnosis of MPM must always be based on immunohistochemical examination. It is recommended to use two markers with positive diagnostic value for mesothelioma (anti-calretinin, anti-WT1, anti-EMA or anti-CK5/6) and two markers with negative diagnostic value to validate the diagnosis (such as anti-Ber-EP4, anti-TTF1 or monoclonal anti-CEA). A review by an expert panel of independent and experienced pathologists to confirm the diagnosis of mesothelioma is sometimes warranted.

Electron microscopy: is not routinely needed to confirm the diagnosis but is of value for epithelial tumours when immunohistochemical results are discordant, and in some sarcomatoid tumours. The presence of long, thin microvilli is highly suggestive of mesothelioma.

Blood and pleural biological markers (Biomarkers): though not yet widely available or routinely requested, biomarkers for MPM are a growing area of interest. Mesothelin is a glycoprotein expressed on the cell surface of normal mesothelial cells, and is over expressed in mesothelioma and various carcinomas. Soluble mesothelin (SM) or SM-related peptides (SMRP) has emerged as a promising potential biomarker for MPM. SM levels are greatly increased in the serum and pleural effusions of patients with MPM compared with healthy asbestos-exposed subjects, or patients with benign pleural lesions or pleural metastasis. Serum and pleural fluid SM showed excellent sensitivity (70–80%) and specificity (80–100%) as diagnostic markers for MPM. However, SM does not capture sarcomatoid and some biphasic mesotheliomas, thus limiting its use a sole diagnostic marker. It is suggested that the association of pleural abnormalities and high SMRP level in newly presenting subjects should be aggressively investigated to exclude mesothelioma or metastatic malignancies. Moreover, since SMRP levels correlate with progression or regression of the tumour, they may be useful in monitoring therapy.

What treatment options would you consider?

MPM does not have one widely accepted treatment modality since none reliably result in cure. Moreover, there is a paucity of randomised clinical trials comparing treatment regimens in this disease.

VATS not only permits directed biopsy but at the same time effusions can be drained, loculations lysed and pleurodesis accomplished usually with aerosolised talc. VATS pleurodesis by itself does not prolong survival, but is preferred in patients with co-morbidities or advanced stage disease, who may then undergo systemic chemotherapy.

Surgical approach includes the more radical complete surgical extrapleural pleurectomy (EPP), which is theoretically the most effective treatment or a debulking cytoreductive pleurectomy/decortication (P/D) procedure that results in removal of the vast bulk of the tumour but leaves microscopic tumour behind. The consensus among centres is that surgery, whether radical or debulking, is best performed in combination with adjuvant chemotherapy, radiotherapy, immunotherapy or other treatments.

However, most patients with MPM have a disease that is not amenable for radical surgery. Palliative surgery may help manage recurrent pleural effusion and radiotherapy may alleviate pain or reduce chest wall masses but the only type of treatment demonstrated by randomised trials to prolong survival is systemic chemotherapy in patients with performance status 0–1. Single agent vinorelbine and combination mitomycin, vinblastine, cisplatin (MVP) have estimated median and 1-year survival rates of 8.5 months and 37% respectively. More recently cisplatin plus pemetrexed has demonstrated a statistically significant survival advantage (12.1 months) versus cisplatin alone (9.3 months) in eligible patients. Other drugs that have also shown activity in MPM include doxorubicin, epirubicin, mitomycin, cyclophosphamide and ifosfamide. There are no standard second line treatment options for advanced MPM; most commonly used agents are gemcitabine, vinorelbine, doxorubicin and irinotecan. Ranpirnase, an antitumour ribonuclease, is a novel agent under investigation for second line treatment of MPM.

Radiotherapy in MPM is used to help relieve pain as well as to treat localised chest wall recurrences. It is also used prophylactically to prevent the seeding of tumour cells along sites of invasive procedures, such as needle biopsy tracks, thoracoscopic incisions and chest tube drainage sites. It can also be used as an adjunct to surgery as hemithoracic adjuvant radiotherapy after EPP, for treatment of the entire resected hemithorax or for treatment of known residual localised unresected tumour. It can be delivered by conventional techniques or with intensity modulated radiotherapy.

CASE BASED DISCUSSION: MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Multiple choice questions

True or false to the following questions.

1. Possible aetiological agents that have been linked with causing malignant mesothelioma include:

a. Asbestos.
b. Erionite.
c. Simian virus (SV40).
d. Radiation exposure.
e. Genetic susceptibility.

2. The following conditions are associated with asbestos exposure:

a. Pleural plaques.
b. Lung cancer.
c. Benign pleural effusions.
d. Diffuse pleural thickening.
e. Cryptogenic fibrosing alveolitis.

Answers

1.

a. True.
b. True.
c. True.
d. True.
e. True.

Asbestos, a naturally occurring fibrous silicate, is the principal carcinogen. It comprises fibrous minerals that are divided into two basic groups: the serpentine fibres (long and curly fibres) which include chrysotile; and the amphibole fibres (straight, short, needle-like fibres) which include crocidolite, tremolite, anthophyllite, and amosite. Risk of mesothelioma increases with (i) fibre burden in the lung; (ii) time since exposure; and (iii) fibre type. In general, the smaller and straighter the fibre the more harmful it is, i.e. crocidolite (blue asbestos) is associated with the highest risk of MPM, chrysotile (white asbestos) has the lowest and amosite (brown asbestos) carries an intermediate risk.

A non-asbestos mineral, erionite has also been identified in Turkey, and has been shown to have a greater carcinogenic potential than asbestos. Simian virus (SV40) is a DNA tumour virus that contaminated US human polio vaccines between 1955 and 1963, and has been shown to cause malignant mesothelioma in 100% of hamsters when injected intrapleurally. However, the general consensus is that SV40 alone does not cause mesothelioma, but may act as a cocarcinogen with asbestos. Cases of MPM with no history of asbestos exposure are commonly reported and these are thought to be due to radiation exposure. The possibility of genetic susceptibility has also been proposed.

2.

a. True.
b. True.
c. True.
d. True.
e. False.

Pleural plaques are a marker of exposure to asbestos and alone rarely if ever lead to symptoms. Often they are noticed incidentally on a chest X-ray taken for a different reason. Asbestos acts alone and synergistically with tobacco in increasing the risk for lung cancer. Diffuse pleural thickening refers to more extensive fibrosis of the pleura than is seen with circumscribed pleural plaques. Benign pleural effusions are also commonly seen in patients exposed. Though asbestosis is caused by asbestos exposure, cryptogenic fibrosing alveolitis is not.

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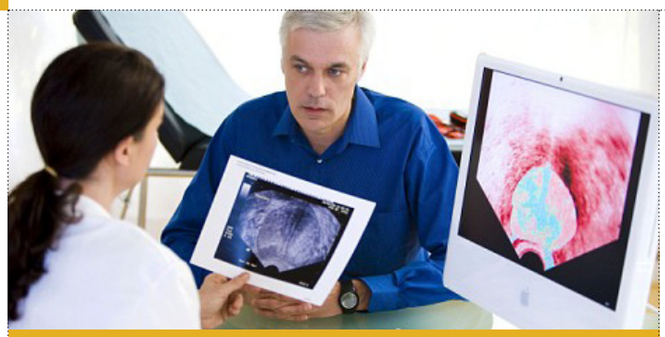
PROSTATE CANCER SCREENING: THE ONGOING DEBATE

Faith McMeekin



There is much ongoing debate about whether there should be a national screening programme in place for prostate cancer, as it is now the most common cancer diagnosed in men.
Good Clinical Care.

Abstract

There is much ongoing debate about whether there should be a national screening programme in place for prostate cancer, as it is now the most common cancer diagnosed in men. This article outlines a very common scenario when patients diagnosed with prostate cancer question why no such screening is in place. An overview of two influential studies – the United States, the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial; and the European Randomised Study of Screening for Prostate Cancer (ERSPC) in conjunction with a summary of the current international guidelines on prostate cancer screening will enable you to answer such a question.

Case history

A 67-year-old gentleman presented to his GP with worsening lower urinary tract symptoms (LUTs) of poor flow and nocturia. On referral to Urology he was found to have Gleason grades 3 and 4 localised prostate cancer and underwent radical prostatectomy. During his postoperative follow-up for erectile dysfunction he asked me "why is there no screening programme for prostate cancer, when women have both breast and cervical cancer screening?" To which I found that I did not have the evidence to support my answer. Currently there is no prostate cancer screening in the UK. This article outlines the evidence to suggest why no such screening programme exists.

After reading this article you will be provided with the evidence to answer such a question should you be asked in the future.

Discussion

Screening for cancer has become common place in the world of modern medicine. Screening for breast, cervical and colorectal cancer is normal practice in some countries, and will no doubt become routine in the future[1–3]. Screening for prostate cancer is an ongoing debate that clinical trials are beginning to ascertain the evidence to establish if indeed it should be introduced here in the UK.

In the United States, most men over the age of 50 years have had a prostate specific antigen (PSA) test despite the absence of evidence from large, randomised trials showing a net benefit[4]. Interestingly 95% of male urologists over the age of 50, report having had a PSA test themselves[5].

The discovery of PSA revolutionised the diagnosis and management of benign and malignant diseases of the prostate. Although not an ideal tumour marker, it is the most widely used marker in the diagnosis and follow-up of any cancer[6]. PSA was first measured quantitatively in the blood by Papsidero in 1980, and Stamey carried out the initial work of the clinical use of PSA as a marker of prostate cancer[7].

Serum concentrations of prostate specific antigen have been widely used for early detection of prostate cancer[8] and this is the clinical area that I am going to focus on, so that if asked by patients/relatives about prostate cancer screening, you can be prepared to give the most accurate answer.

Using our case study it is apparent that he, with the benefit of a retrospective view and a diagnosis of prostate cancer, wanted to know why there is no screening in place for prostate cancer?

There are two main clinical trials that have set out to answer this question and that many observers hoped would settle the controversy that exists. In the United States the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial reported no mortality benefit from combined screening – PSA testing and digital rectal examination during a median follow-up of 11 years. In the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial, they report that PSA screening without digital rectal examination was associated with a 20% relative reduction in the death rate from prostate cancer at a median follow-up of 9 years, with an absolute reduction of about 7 prostate cancer deaths per 10,000 men screened. For a comparison of trial design, study population and outcomes see Table 1.

PROSTATE CANCER SCREENING: THE ONGOING DEBATE

Faith McMeekin

	PLCO	ERSPC
Patient number	76,693	162,243
Average age	55–74 years	55–69 years (mean 60.8)
Population	10 US study centres	7 European countries muliticentre
PSA screening timing	Annual for 6 years	Once every 4 years
Digital rectal exam†	Annual for 4 years	Dependent upon PSA
Screening PSA cut-off‡	4.0ng per millilitre	3.0ng per millilitre
Primary outcome assessed	Rate of death from prostate cancer	Rate of death from prostate cancer
Incidence of prostate cancer screening group	116 per 10,000 person years	8.2% cumulative incidence
Incidence of prostate cancer control group	95 per 10,000 person years	4.8% cumulative incidence
Conclusions	Rate of death from prostate cancer very low and no significant difference between two study groups	PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with overdiagnosis

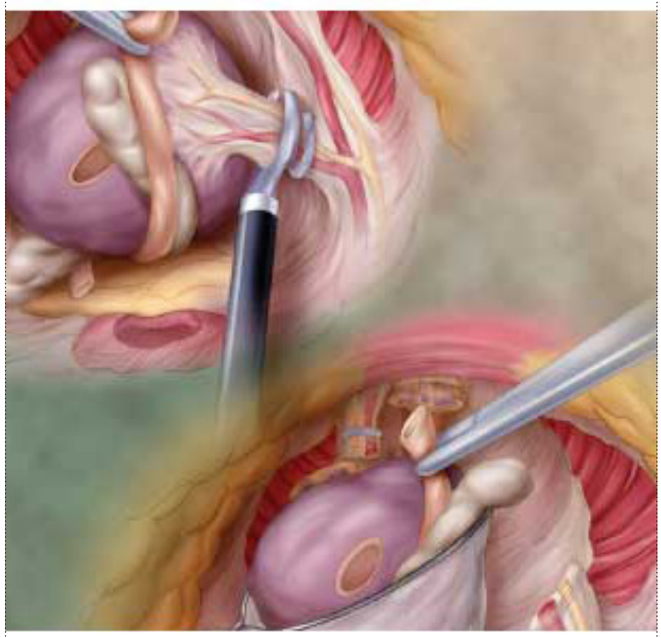
Table 1: Summary of the findings of PLCO and ERSPC studies.
† PLCO study 86% compliance.
‡ The PSA at which patient was referred for biopsy.

As can be seen, the two trials are quite different in their design and also in their conclusion. Furthering the debate and ambiguity surrounding PSA testing and not allowing for clarification to assist the physician in reassuring patients why such a screening programme does not exist here in the UK.

As can be seen both are very extensive trials entailing good numbers of patients but there are some very important considerations:

1. Trial design: very different study populations, a large proportion of the American subjects, despite being in the control arm had had previous PSAs giving an element of "contamination" and this might be responsible for the apparent lack in significant difference between the control and screening group mortality,

2. Incidence versus mortality: despite an increasing incidence of prostate cancer, the age-standardised prostate cancer mortality has decreased in many countries around the world with or without early detection programmes. For example, between 1989 and 2003 the age-standardised incidence rate of prostate cancer increased by 48.4% (93.2 cases per 100,000 men) in the Netherlands, in this same time period mortality rates fell by 11% (28.4 deaths/100,000 men) **http://www.cancer.gov.**



3. Efficiency of screening: the usefulness of a screening test is determined by how well it predicts disease, with prostate cancer this is very much unknown. Screening results in more frequent detection of small volume, low grade and organ confined prostate cancers, which are diagnosed earlier in their course[9, 10]. It is unknown if these cancers would have become significantly symptomatic over time or if indeed the subject would die of other causes, without any treatment ever being required for their disease, leading to over-diagnosis/over-treatment.

4. Over-diagnosis: this is diagnosing tumours that would have otherwise remained clinically unrecognised and would only be discovered when the individual died from other causes. Ideally with a good screening test we would hope to avoid identifying indolent tumours that would not have caused any significant harm in the patient's lifetime[11]. Over-diagnosis appears to be particularly harmful when it results in invasive treatment of the tumours that would unlikely to be harmful – defined as over-treatment.

5. Over-treatment: it is important to recognise this when considering any screening test, in particular with radical treatment for prostate cancer comes some well recognised morbidities, for example, erectile dysfunction and incontinence. Unnecessary invasive treatment with respect to the outcome of the natural course of the tumour within its host is essential not to over-treat. A number needed to treat analysis of the benefit of radical treatment of all newly diagnosed favourable-risk prostate cancer patients, compared with a strategy of active surveillance with selected delayed intervention was presented by Klotz[12]. This suggested that approximately 73 patients will require radical treatment for each prostate cancer death averted.

PROSTATE CANCER SCREENING: THE ONGOING DEBATE

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In addition to the evidence it is essential to use the current guidelines available as outlined in Table 2[13].

American Cancer Society: does not support routine testing for prostate cancer. Recommends discussion with doctor regarding benefits and limitations of early detection with an offer of a PSA test beginning at : • Age 50 for average-risk men with life expectancy of at least 10 years. • Age 45 for men at high risk of developing prostate cancer (African-Americans and men with first degree relative who had prostate cancer diagnosed younger than age 65). • Age 40 for men with several first degree relatives who had prostate cancer at an early age. If, after discussion, a man asks his health care professional to make the decision for him, he should be tested (unless there is a specific reason not to test)
American Urological Association: PSA test should be offered to well-informed men aged 40 years or older who have a life expectancy of at least 10 years.
Cancer Council Australia: no recommendation for or against prostate cancer screening. Men should weigh the pros and cons before deciding to be screened.
European Urological Association: current published data are insufficient to recommend population screening for prostate cancer as a public health policy owing to large over-treatment effect.
Japanese Urological Association: the evidence for the effect of prostate cancer screenings is insufficient. PSA and digital rectal examinations are not recommended for population-based screening programmes.
NHS (UK): no organised screening programme for prostate cancer but the informed choice programme, Prostate Cancer Risk Management, aims to provide high quality information about the risks and benefits to men who ask about screening in order to enable them to decide whether to have the test.

Table 2: International recommendations on screening for prostate cancer.

Given the current evidence, I would support the opinion of the European Urological Association, that data on costs and benefits remain insufficient to support population-based screening. The financial and psychological costs of false positive results, over-diagnosis and over-treatment of prostate cancer need to be measured more precisely. The most important consideration is to fully understand the implications of checking a patient's PSA and for him to understand that the test cannot tell whether they have a life-threatening cancer but it could lead to tests/treatments they might better have avoided[13].

When we look back to the case study it is not a straightforward question to answer, but armed with the evidence laid out in this article, I think that it is possible to appreciate that there isn't a screening programme in the UK for prostate cancer at this moment in time for good reason – the evidence base to support it is not there to make it compliant with the basic tenets of screening programmes laid out by the World Health Organisation.

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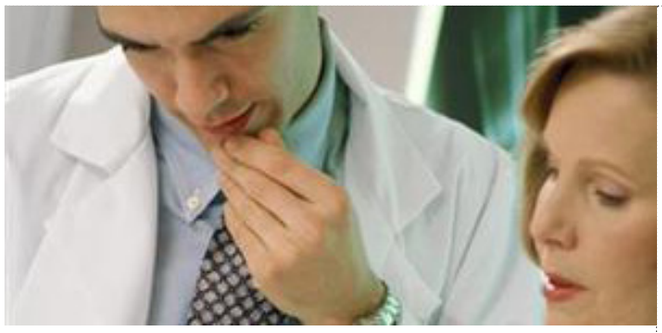
REFLECTIVE PIECE

Karl Payne



I had been working as an F1 doctor for a mere 48 hours, it was a Thursday; outside it was sunny, but on the ward a storm was brewing.

My consultant was covering surgical admissions and a patient had been presented the previous day with suspected bowel perforation, most likely a perforated diverticulum. To complete the story, this was a 58-year-old dishevelled lady who was currently living in a women's shelter and had a history of severe personal life trauma. The best course of action was immediate surgery, unfortunately the patient never made it to theatre.

Mid-morning the patient was refusing any investigations and totally refusing surgery, claiming she "felt much better and was on the mend". My consultant and the locum registrar tried at length to counsel the patient on the consequences of her refusing surgery, but to no avail and she continued to refuse any intervention. By mid-afternoon it seemed she had eventually seen the light, and agreed to surgery. The emergency theatre was booked and the locum registrar returned at around 5pm to consent the patient, but suddenly she once again refused any treatment. This game of cat and mouse had been happening all day and understandably all involved were exceptionally frustrated, none more so than the locum registrar who was visibly fuming.

The notes slammed on the desk, he uttered a muffled profanity and returned to the doctors mess. At that moment a wave of responsibility swept over me the likes of which I had never before experienced, and it was left to me to deal with this patient. My SHO hadn't started work yet and my consultant was busy elsewhere. I felt somewhat empowered but also somewhat abandoned, and I quickly realised why my finals practical exam 3 months ago hadn't included a section on counselling a homeless patient who was flatly refusing any form of treatment!

It was clear the patient wasn't quite registering the warnings we had given about the consequences of refusing surgery, there was a subtle sense of confusion that you couldn't quite define. My attempts at communicating the risks involved seemed to fall on deaf ears, and I was frustrated that I couldn't get the patient to see sense and take on board my warnings. It was decided a psychiatric review was needed, and it was my job to find a psychiatrist. Suddenly I wasn't a medical student skulking on the wards, but a medical professional charged with the assignment of executing an important task. I tried for over an hour to find a psychiatrist, every number rang unanswered and every bleep was unreturned. I reviewed the patient and she was stable, which only served to polarise her views of not needing surgery.

Having been at work for nearly 12 hours I was running on empty, and desperately hungry. I made a hospital at night referral and resigned myself to defeat; this matter would have to be settled in the morning.

At this point I must send out a plea for sympathy from any fellow FY1 who has attempted to obtain a psychiatric review for a patient; and not only that but a review on a surgical patient at 7pm. Second, I apologise to the psychiatrists who must receive a multitude of referrals from surgeons trying to cover themselves from a medico-legal standpoint.

Walking to my car I remembered my balding ethics lecturer discussing autonomy and non-maleficence, and I was plagued by feelings of guilt and frustration. Had I done everything in my power to persuade the patient into surgery but, on the other hand, is that my job?

As I reflect on my first few months as a newly qualified doctor, be it talking among friends or a moment of clarity with a chilled lager in my right hand; I can identify this simple yet poignant moment as a definitive event in the moulding of my early perceptions.

It was the first time I felt different from being a student, I had a purpose; and I imagine other FY1s and surely all doctors can identify such moments early in their career. I realised the steep learning curve I was on and how medicine isn't black and white like a text book, but a hazy grey of indecision and compromise.

Since then my team has come together and I am both pleased and relieved that in a similar situation I would have an SHO and registrar to help me out. Many an occasion has arisen when I've learnt that it's not only during your ABCDE approach that you call for help! If events were again to unfold in a similar manner, I believe I would have the experience to remain calm but to also retain my objectivity. At the time I overestimated the gravitas of the situation, and perhaps that is why it had such an emotional impact; it seems to be the hardest thing to present treatment options in an unbiased way and not as an American sitcom lawyer. Patients have the right to choose and nothing reminds me of this more than seeing an amputee patient outside the hospital doors lighting up a cigarette.

In conclusion; the patient never did agree to surgery, she was treated conservatively and gradually deteriorated. Around a month later she became septic and very sadly died.

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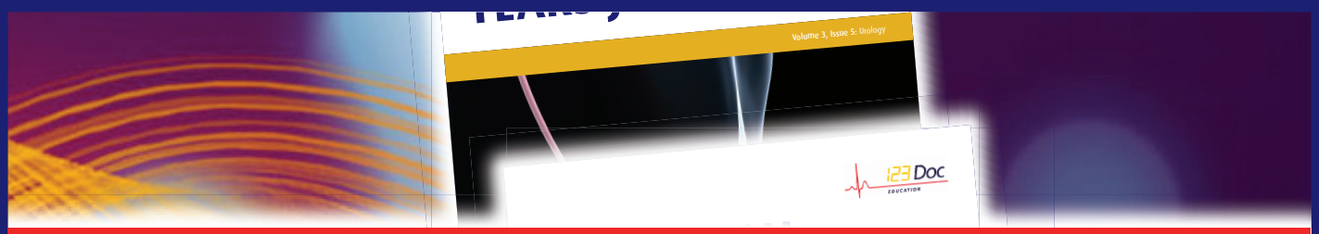

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