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Leukaemia update. Part 2: managing patients with leukaemia in the community

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Although curative chemotherapy is typically delivered in the inpatient setting, patients are at home for substantial periods of time while they progress through treatment. Patients with chronic leukaemia are usually treated entirely as outpatients. Almost all of these patients will develop complications from their disease or its treatment, and after completing chemotherapy, some patients will experience late complications. A balance between hospital and community based care is vital to optimise treatment efficacy and avoid unnecessary hospital admissions. This article reviews some of the adverse effects of leukaemia chemotherapy that non-specialists should be aware of and considers the longer term problems seen in survivors.

SOURCES AND SELECTION CRITERIA

We searched PubMed for clinical trials and the Cochrane Library for meta-analyses. We also sought expert opinion from experienced consultant haematologists. Keywords used were leuk(a)emia, chemotherapy, supportive care, and community care. We also reviewed guidelines from the British Committee for Standards in Haematology and the National Institute for Health and Clinical Excellence.

Supporting patients with leukaemia through chemotherapy

Treatment and prevention of infection including neutropenic sepsis

Neutropenic sepsis is a medical emergency, and prompt treatment with intravenous antibiotics is usually life saving.[1] Although incidence depends on regimen intensity, all patients on chemotherapy are at risk. Patients may present with non-specific symptoms, rigors, or symptoms associated with the infection site. Patients are advised to contact the acute oncology service available at their local treatment centre, and to monitor their temperature if they feel unwell. The National Institute for Health and Clinical Excellence (NICE) defines neutropenic fever as a temperature greater than 38°C in a patient having anticancer treatment whose neutrophils are 0.5×10^9/L or lower. If febrile neutropenia is suspected, patients are advised to attend the emergency department for urgent intravenous antibiotics. If the neutrophil count is unknown, neutropenia is assumed until proved otherwise. Paracetamol can mask fever in patients undergoing chemotherapy and is therefore avoided.

NICE recommends piperacillin and tazobactam empirically in the absence of contraindications, unless local microbial resistance patterns dictate otherwise.[1] Patients who are systemically well, without an infective focus, and non-neutropenic are at lower risk of septic complications. These patients may be discharged on oral antibiotics, as in NICE guidelines (moderate quality evidence) after appropriate investigations and cultures, with a clear plan to follow up microbiology results and patient progress.[1] Because glucocorticoids can suppress fever and are included in many regimens, absence of fever may not exclude "cold sepsis" in patients on chemotherapy.[1]

The highest risk of sepsis is during the neutrophil nadir ($<0.5\times10^9$/L), which usually occurs one to two weeks after chemotherapy.[1] In our centre, systemically well patients who have completed treatment with documented sustained neutrophil recovery are considered to be at low risk, and a full blood count can be performed in the community to investigate febrile episodes. In cases of doubt, patients and general practitioners can contact their local acute oncology service.

Certain evidence based practices can reduce infections in patients receiving chemotherapy. A recent meta-analysis confirmed that, in patients fulfilling certain criteria, such as those with a history of long inpatient stays owing to neutropenic sepsis, subcutaneous granulocyte colony stimulating factor can reduce time in hospital.[2] This factor is given subcutaneously and promotes neutrophil maturation. Although most patients learn to self inject, the help of a district nurse may be needed. To minimise the risk of bacteria entering the bloodstream, consensus recommends that digital rectal examination is avoided in patients undergoing chemotherapy.[3] British Committee for Standards for Haematology (BCSH) guidelines for patients with chronic lymphocytic leukaemia recommend influenza, pneumococcal, and *Haemophilus influenzae* vaccinations,[4] although responses are often suboptimal due to immunosuppression.[5] For optimal uptake, vaccination is ideally given more than two weeks before or six months after chemoimmunotherapy.[4] Live vaccines are avoided, unless given to re-establish immunity after stem cell transplantation. In our centre, the transplant team advises GPs on vaccinations for individual patients, but global practices vary.

SUMMARY POINTS

- Neutropenic fever is a medical emergency and should be suspected in all unwell patients with leukaemia
- Leukaemia and its treatment can affect all organ systems
- Chemotherapy can cause psychological disturbances that require a multidisciplinary approach
- Optimal support for patients with leukaemia involves a balance of community and hospital based care
- Most intercurrent drugs can be continued throughout leukaemia treatment. Warfarin is usually changed to low molecular weight heparin and antihypertensives may be stopped during septic episodes; antiplatelet drugs are usually stopped if safe

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- Malignant and premalignant lesions of the penis (*BMJ* 2013;346:f1149)
- Postpartum management of hypertension (*BMJ* 2013;346:f894)

Box 1 | Cytopenias that are likely to be clinically significant

Haemoglobin <100 g/L with symptoms of anaemia

Platelets <50×10^9/L: patients with platelets <10×10^9/L will probably need a platelet transfusion

Neutrophils <1×10^9/L: patients with neutrophils <0.5×10^9/L are at higher risk of life threatening sepsis

The need for antimicrobial prophylaxis is strongly regimen dependent, and prophylaxis is usually managed by the haematologist. Elective dental procedures are ideally avoided in patients on intensive chemotherapy, particularly in those with mucositis. A comprehensive review of prevention and treatment of cancer related infections is available from the National Comprehensive Cancer Network (NCCN).[6]

Patients embarking on intensive chemotherapy with curative intent will usually have an indwelling venous catheter inserted to facilitate drug delivery, minimise extravasation risk, and avoid discomfort. Superficial infections around the entry site are not uncommon, with a frequency of 0.08-19 per 1000 catheter days, and line related sepsis can occur.[7] Erythema or discharge around the entry site should alert doctors to the possibility of infection. These catheters increase the risk of thrombosis. Regular line maintenance is needed to minimise risks of thrombosis and infection. This usually involves scheduled dressing changes and heparin flushes by trained professionals using aseptic techniques according to local protocols. Suspected problems related to the catheter should be dealt with urgently by the specialist team, who can be contacted through the acute oncology service.[7]

When are blood products appropriate during chemotherapy?

Thrombocytopenia and anaemia occur in virtually all patients on intensive chemotherapy, and these patients will require at least one transfusion at some point. Fewer than 10% of patients on non-intensive treatment require transfusions.[8] Although published data are lacking, consensus BCSH guidelines—developed by an expert task force from best available evidence and reviewed by the Royal Colleges of Physicians, Surgeons, and Anaesthetists—indicate that patients with platelets under 10×10^9/L are at risk of serious bleeding and usually require platelet transfusions. Platelets are indicated for febrile patients with counts under 20×10^9/L, those with haemorrhagic symptoms and platelets under 50×10^9/L, and patients who are bleeding and on antiplatelet drugs regardless of platelet count.[9] Non-steroidal anti-inflammatory drugs cause irreversible platelet dysfunction and are thus avoided in patients with leukaemia. Closely monitor patients on prophylactic antiplatelet agents, including selective cyclooxygenase-2 inhibitors, for signs of bleeding and review the need for continued prophylaxis.

On the basis of BCSH consensus guidelines, red blood cell transfusion is considered when haemoglobin drops below 100 g/L in patients with cardiac or pulmonary disease. In patients without cardiopulmonary disease, transfusion is considered when symptoms develop, although most clinicians would transfuse patients with haemoglobin below 70 g/L.[10] A retrospective study in leukaemia patients found no evidence of adverse effects with a restrictive transfusion policy (haemoglobin threshold of 88 g/L, depending on age and symptoms) versus a liberal policy (threshold of 96 g/L).[11] Patients with recurrent clinically significant cytopenias (box 1) may require reduction, delay, or discontinuation of chemotherapy, a decision that is usually made by the haematologist.

What are the common side effects of chemotherapy for leukaemia?

Gastrointestinal disturbances are common, affecting about 30% of patients on non-intensive regimens[8] and all patients on curative regimens.[12] Chemotherapy induced nausea and vomiting can usually be minimised with prophylactic antiemetics, and guidelines are available through the NCCN (based on expert consensus and non-randomised data).[13] Initially, the dopamine antagonist domperidone is often used, although some patients on mildly emetogenic regimens such as oral chlorambucil may only need metoclopramide or cyclizine. Patients on highly emetogenic protocols are often started on dexamethasone or ondansetron. A meta-analysis of 7808 patients demonstrated the efficacy of serotonin receptor antagonists, such as ondansetron and granisetron.[14] Domperidone and ondansetron are often combined.[13] Aprepitant belongs to a new antiemetic class of neurokinin receptor 1 antagonists and prevents the binding of substance P to the NK1 receptor. It is available for patients whose symptoms persist despite standard antiemetics, and its efficacy in chemotherapy induced nausea and vomiting was shown in a meta-analysis of more than 8500 patients. NK1 receptor antagonists reduced the relative incidence of breakthrough nausea by 50%.[15] Appropriate management of symptoms is vital to prevent dehydration and renal impairment because many chemotherapy drugs are renally excreted.[16]

Constipation is common—for example, 15-20% of patients on vincristine regimens will develop moderate to severe constipation.[17] Prompt management with laxatives can help prevent compromising patients' nutritional intake. Randomised controlled trials on the optimal management of constipation in patients on chemotherapy are lacking,[18] and local protocols vary. In our centre, a gentle laxative such as ispaghula, lactulose, or senna is initially tried, progressing to stronger bowel stimulants such as co-danthramer or bisacodyl if necessary.[19] Co-danthramer is licensed for this use only in terminally ill patients so is used in extreme cases only, usually in the hospital setting, often in consultation with a palliative care specialist. Although uncommon, intestinal pseudo-obstruction can occur. It sometimes requires the administration of an enema, which introduces the risk of infection.[20] Patients on chemotherapy who present to GPs with gastrointestinal disturbances are best managed in consultation with a haematologist to optimise symptom control and avoid unnecessary hospital attendance.

Glucocorticoids are integral to many antileukaemic regimens, and it is important for GPs to bear in mind that patients may have steroid related side effects. Steroid induced hyperglycaemia is usually reversible, but patients occasionally require hypoglycaemic agents. In such cases, dosage can be optimised in the community,

and a clear understanding of the causes and expected duration of hyperglycaemia is needed. Other common side effects include insomnia and mood disturbance, which may require a short term sedative or antidepressant. The haematologist usually alters steroid dosages if needed. When necessary—for example, in patients with acute lymphoblastic leukaemia who are on high doses of dexamethasone, proton pump inhibitors and bisphosphonates will be started by the specialist team and stopped when appropriate. For convenience, patients may be advised to obtain repeat prescriptions from their GP.

How should comorbidities be managed in leukaemia?

Because most leukaemias present in later life, patients often have comorbidities. Most intercurrent drugs are continued, with some notable exceptions. Patients on warfarin are often converted to low molecular weight heparin, particularly if intensive chemotherapy is planned, to avoid fluctuations in international normalised ratio owing to altered warfarin metabolism.[21] During septic episodes antihypertensives may be stopped to minimise hypotension and subsequent acute tubular necrosis. After recovery from a septic episode, resumption of antihypertensives is considered, depending on blood pressure reassessment. Antihypertensives can be reinstated after chemotherapy is completed and the risk of sepsis has subsided. The haematologist and GP or relevant specialist should discuss any uncertainty related to drugs.

What psychological support is available?

The diagnosis of leukaemia usually has negative psychological connotations. Patients often require hospital admissions, necessitating time off work and school. In a recent quality of life substudy of the large CLL4 trial, leukaemia patients often described themselves as having lost their role in society through not being able to work and socialise normally. Depending on the chemotherapy regimen, 29-60% of trial participants reported significant deteriorations in social functioning and fatigue on health related quality of life questionnaires while on treatment.[22] Clinically significant depression can be precipitated or exacerbated by a diagnosis of leukaemia.[23] Haematologists are not experienced in dosage titrations of antidepressants and may request input from the GP, or occasionally a psychiatrist, to manage psychological disturbances.

Haematology clinical nurse specialists play a major role in supporting patients during this difficult time, helping patients and their families cope with diverse psychosocial problems, ranging from impending death and bereavement to difficulty obtaining travel insurance. These nurses have a broad role and are often the member of the multidisciplinary team with the most frequent contact with the patient. In our centre, they are the first contact point for patients who become unwell at home and are vital in coordinating hospital and community care.

Survival after chemotherapy

Patients treated for chronic leukaemia will usually be followed up by a haematologist for life. Patients with acute leukaemias who are well three to five years after completing treatment can be considered cured and discharged, depending on local protocols. The transition from a routine of hospital visits and highly supported environments to outpatient follow-up is often stressful. About 15% of young survivors of leukaemia report disrupted sleep,[24] and over 50% of older survivors report fatigue.[23]

Eventually many patients resume full time work. For motivated individuals we recommend a gradually escalating exercise programme with gentle activities such as walking and swimming, as recommended by cancer support services such as Macmillan in the United Kingdom, but we also counsel patients that levels of pretreatment physical fitness may not return.

Chemotherapy related second cancers

A large study of more than 420 000 patients on US cancer registries showed that patients who have received chemotherapy for any cancer are on average 4.7 times more likely to develop acute myeloid leukaemia than the general population.[25] These leukaemias usually present insidiously and can occur more than 10 years after treatment has stopped. Myelodysplasia progresses over several months and is characterised by gradually worsening cytopenias and dysplastic appearances on the blood film.[26] There are currently no nationally established screening programmes for second cancers in leukaemia survivors. We recommend a low threshold for requesting a full blood count and blood film for cancer survivors presenting with non-specific symptoms.

End organ damage

Chemotherapy drugs can affect any organ system and can cause toxicity years after treatment stops. Vinca alkaloids cause peripheral neuropathy that usually develops during treatment and can often be reversed by reducing the dose. Permanent neuropathy with chronic superficial neuropathic pain can occur. This may respond to lidocaine infused pads, which carry a strong recommendation from BCSH based on randomised clinical data, or to gabapentin and amitriptyline.[27] Cardiomyopathy is a documented late effect of anthracyclines and can progress to cardiac failure. Observational studies of leukaemia survivors have also shown an increased incidence of hypothyroidism, hypogonadotrophic hypogonadism, insulin resistance, and dyslipidaemia.[28]

Although most recipients of allogeneic stem cell transplants will be followed up at a specialist centre, GPs may

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

British Committee for Standards in Haematology (www.bcshguidelines.com)—Specific guidance on leukaemia treatment is available in the Haemato-oncology section and advice on blood transfusion in the Transfusion section

National Comprehensive Cancer Network (www.nccn.org)—Free guidelines no registration required

Resources for patients

Macmillan (www.macmillan.org.uk)—Information on treatment

Leukaemia and Lymphoma Research (www.leukaemialymphomaresearch.org.uk)—General information on leukaemia

Box 2 | Common side effects of chemotherapy (dependent on regimen)

Short term

Myelosuppression: Infection, bleeding, anaemia

Gastrointestinal: Nausea, vomiting, constipation, diarrhoea, mucositis

Neurological: Peripheral neuropathy, psychological disturbances

Metabolic: Electrolyte derangement, tumour lysis syndrome, nephrotoxicity, hepatotoxicity

Cutaneous: Hair loss, rashes

Long term

Second cancers

Subfertility

Cardiomyopathy, neuropathy, endocrine dysfunction

Chronic graft versus host disease (allogeneic transplant recipients only)

FUTURE RESEARCH

Next generation sequencing methods are being used to elucidate the pathogenic mutations in leukaemia and identify potential future drug targets

Pilot schemes for the delivery of chemotherapy in the community have been established across the UK

New targeted therapies such as ibrutinib and GS-1101 are entering clinical trials in the UK

TIPS FOR NON-SPECIALISTS

Refer patients with leukaemia and a temperature of more than 38°C to the emergency department without waiting for a neutrophil count

Mucosal bleeding caused by leukaemia or its treatment will probably require blood product transfusion

Flu and pneumococcal vaccinations are indicated in patients with leukaemia; avoid live vaccines

Most intercurrent drugs can be continued throughout leukaemia treatment

encounter chronic graft versus host disease, which occurs in about 30% of allograft recipients, and can have protean manifestations. Patients may present to their GP believing that their symptoms are unrelated to the allograft. Symptoms that should alert generalists to this disease include progressive breathlessness due to bronchiolitis obliterans, skin rashes, xerophthalmia, xerostomia, dysphagia, myositis, and peripheral neuropathy. According to BCSH guidelines, symptoms can be treated with immunosuppression, and an early visit to the transplant clinic is indicated.[29] The transplant team can be reached through the local acute oncology service and can offer advice to GPs for transplant patients with new unexplained symptoms.

Subfertility

Subfertility is a major problem for younger patients with leukaemia. A recent large retrospective Scandinavian study of young survivors of leukaemia showed a successful pregnancy rate 25% lower than in the general population.[30] Sperm storage is offered to men of reproductive age who have not yet completed their families who undergo intensive chemotherapy in the UK, but cryopreservation of embryos or mature oocytes is not widely available. Previous chemotherapy is a potential causative factor when couples present with fertility problems.

Box 2 lists the common side effects of chemotherapy.

What's next for leukaemia treatment?

Because chemotherapy demands are increasing by 15% annually, chemotherapy delivery services have been developed to administer treatment in GP surgeries, community hospitals, nursing homes, and patients' homes. The advantages for patients include increased choice, more personalised care, and reduced waiting times. There are concerns that less back-up will be available compared with traditional oncology day units. However, by transferring administration of the less complex chemotherapy regimens to the community under the auspices of senior chemotherapy nurses, it is hoped that the need for on-site medical personnel will be minimised. In the UK, the Department of Health has issued guidance for primary care trusts on the development of such services in an effort to meet the rising demand for modernised cancer care, as is currently happening in the United States and the NHS East of England regional pilot programme.[31]

A unifying goal for cancer treatment is to move from cytotoxic chemotherapy to targeted treatments. Chronic myeloid leukaemia provides the best example of a highly toxic regimen having been replaced by a single daily tablet in most patients. Other examples in development include a chemotherapy-free regimen combining retinoic acid and arsenic trioxide for selected patients with acute myeloid leukaemia, as in the ongoing MRC AML-17 UK national randomised clinical trial. Early phase trials of ibrutinib, a tyrosine kinase inhibitor targeting downstream signals from the B cell receptor, have shown promising results in chronic lymphocytic leukaemia, and the phosphatidylinositol 3 kinase delta inhibitor, GS-1101, entered phase III trials in 2012.[32 33] As these new treatments are nearing the bedside, advanced high throughput genomic sequencing methods are mapping the leukaemic genome in ever greater detail,[34] paving the way for the development of personalised chemotherapy-free antileukaemic regimens.

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ANSWERS TO ENDGAMES, p 40

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PICTURE QUIZ

Painful blisters on the hand

1 Figure 1 shows large tense bullae with surrounding erythema sparing the index finger. The blisters extend proximally to the metacarpophalangeal joints and affect the volar and dorsal aspects of the fingers (figs 1 and 2).
2 This is an example of blistering distal dactylitis—a superficial bacterial infection of the anterior fat pad of the distal phalanx that presents with large blisters. The differential diagnosis includes cellulitis, bullous impetigo, bullous pemphigoid, herpetic whitlow, herpes zoster, coma blister, thermal injury, allergic contact dermatitis, and fixed drug eruption.
3 Classically, the condition is caused by group A β haemolytic streptococci (*Streptococcus pyogenes*), with some reported cases caused by *Staphylococcus aureus* or *Staphylococcus epidermidis*.
4 The treatment recommended for blistering distal dactylitis consists of incision and drainage of the blisters, followed by a course of antibiotics, usually of 10-14 days' duration.

CASE REPORT

Recurrent hypoglycaemia in a young man without diabetes

1 Insulinoma, factitious hypoglycaemia, adrenal insufficiency (cortisol deficiency), and tumours that secrete insulin-like growth factor.
2 Seventy two hour fasting test, short synacthen test, and localisation studies (such as magnetic resonance imaging and ultrasound of the pancreas).
3 Studies to rule out multiple endocrine neoplasia type 1 (MEN1)—for example, measurement of parathyroid hormone concentrations and pituitary function tests.

STATISTICAL QUESTION

Units of analysis

The child (answer *a*) was the unit of analysis.