Emergencies in leukaemia

A Guide for Nurses

Leukaemia Care
Nurse Academy

Introduction

The management of leukaemia is an emergency in itself, and an efficient and effective diagnostic approach is vital. Rapid assessment of the patient to determine their suitability for treatment of differing intensities is also crucial. However, at diagnosis and relapse, patients often present with urgent complications secondary to bone marrow failure or the treatment of these complications, requiring emergency care.

If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

In this booklet

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Webinars

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

Neutropenic sepsis

Patients with leukaemia are at high risk of infection due to the immune dysfunction caused by the disease itself and cytotoxic treatments. Despite treatment, however, infection can still lead to sepsis, characterised by widespread tissue damage and inflammatory reactions that can cause life-threatening organ dysfunction.

Assessment

Any neutropenic patient with signs of a systemic inflammatory reaction is likely to have sepsis. The signs and symptoms of sepsis include those shown in Table 7.1 (these will vary with age). Neutropenic sepsis is diagnosed in patients undergoing chemotherapy as a neutrophil count lower than $0.5x10^9$/L (500/µL) and a temperature above 38°C, or signs or symptoms of sepsis.

The principal risk factors for sepsis after cytotoxic chemotherapy are the severity and duration of granulocytopenia, the disruption of skin and mucosal barriers, and insertion of catheters.

Treatment

The maximum recommended dose of a broad-spectrum antimicrobial should be given immediately, along with intravenous fluids and oxygen as needed. The infection source needs to be found, and additional antimicrobials against known infections should be administered as appropriate. It is important to assess sepsis complications to ensure timely referral to critical care services for further support if this is appropriate. Further antibiotic and admission management may be guided by using scoring systems to assess the risk of developing further complications.

TABLE 7.1

Signs and symptoms of sepsis

General parameters
• Fever (temperature >38oC)
• Hypothermia (core temperature <36oC)
• Heart rate >90 bpm
• Tachypnoea > 30breaths/min
• Altered mental status
Haemodynamic parameters*
• Arterial hypotension
• Organ dysfunction including acute oliguria and renal dysfunction
Tissue perfusion
• Hyperlactatemia
• Decreased capillary refill or mottling

*In neutropenic patients, WBC count cannot be used to define sepsis.

bpm, beats per minute.

Coagulopathy in acute promyelocytic leukaemia

APML is a rare subtype of AML. It is notable in the modern era by the success of disease-specific treatments, such as ATRA or arsenic trioxide, which have led to impressive improvements in excess of 95% overall survival. However, APML represents a medical emergency, with considerable early morbidity and mortality at the initial diagnosis. This is primarily due to the increased bleeding risk in uncontrolled APML. Trial data suggest an early death rate in the region of 5%. Still, in a population-based study, the early death rate was as high as 28%, particularly because of CNS haemorrhage.

The coagulopathy seen in APML is due to the interaction of several different pathophysiological processes, including activation of the clotting system, increased fibrinolytic activity, cytokine release and non-specific proteolysis, leading to a form of DIC and hyperfibrinolysis. In DIC, increased fibrin deposition blocks small blood vessels; in turn, the increased clotting depletes the platelet levels and clotting factors needed to control bleeding. RBCs are damaged by the microangiopathic process, resulting in the production of red cell fragments. In APML it is the fibrinolytic activity that predominates, with fibrinogen consumption increasing the risk of bleeding (Figure 7.1).

Management of this coagulopathy is twofold:

- rapid instigation of antileukaemic therapy
- meticulous supportive care

Treatment with ATRA should begin as soon as APML is suspected and before a definitive diagnosis is reached. Coagulation should be monitored by daily or twice-daily measurements of prothrombin time, activated partial thromboplastin time, platelet count and fibrinogen levels. Platelet transfusions should be used to maintain platelet levels above 30–50x10^9/L, and fibrinogen levels kept above 1.5g/L by the use of cryoprecipitate.

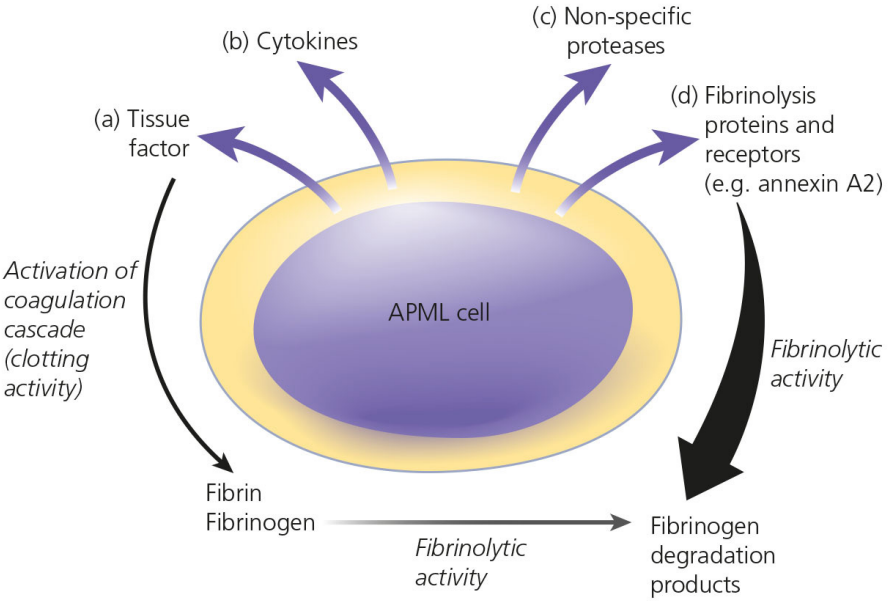

Figure 7.1 Simplified model of the mechanisms underlying the coagulopathy seen in APML. The leukaemic promyelocyte expresses (a) tissue factor, which activates the clotting cascade; (b) cytokines, which induce endothelium thrombogenicity; (c) non-specific proteases, which proteolyse fibrinogen/fibrin and other coagulation factors; and (d) fibrinolysis proteins and receptors that regulate fibrinolysis. Fibrinolysis usually predominates, causing hypofibrinogenaemia and high-risk bleeding.

Tumour lysis syndrome

TLS may arise spontaneously because of the rapid turnover of leukaemic cells, but it occurs more frequently in the first few days after chemotherapy is initiated. The destruction of large numbers of tumour cells results in the rapid release of intracellular metabolites into the extracellular space, overwhelming homeostatic control mechanisms, which leads to hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia. The earliest change is often hyperkalaemia. Subsequent deposition of uric acid crystals in the renal tubules impairs the kidneys' ability to maintain adequate homeostasis of the electrolytes, resulting in a downward spiral.

TLS is potentially life threatening because it can lead to cardiac arrhythmias or acute renal failure, and patients may require organ support in an intensive therapy unit.

Laboratory and clinical tumour lysis syndrome

The formal definition of TLS is based on a review by Cairo and Bishop. They defined laboratory TLS as two or more abnormalities in potassium, phosphate, uric acid or calcium levels. Clinical TLS is present when patients have one of the laboratory criteria and at least one of the following: seizures, acute renal failure, elevated creatinine levels, cardiac arrhythmia or death.

Risk factors

The risk of TLS depends on both patient and disease factors (Table 7.2). For example, elderly patients with pre-existing renal impairment are at an increased risk of TLS. With specific regard to leukaemia, acute leukaemias with high WBC counts (for example, $>100x10^9/L$) are at high risk of TLS when treated with cytotoxic chemotherapy, because of the tumour bulk and rate of turnover.

Management

The approach to managing TLS can be divided into prophylaxis and treatment.

Prophylaxis

As a universal measure, all patients at risk of TLS should be given at least 3L of fluid intravenously over 24 hours to maintain good diuresis. Alkalisation of urine is not

TABLE 7.2

Risk factors for TLS
• Large tumour size
• Tumours with rapidly dividing cells
• Pre-existing renal impairment
• High levels of lactate dehydrogenase
• Increased age
• Treatment with highly active, cell cycle-specific agents
• Concomitant use of drugs that increase uric acid levels

advisable as this may precipitate crystallisation of xanthine and hypoxanthine in the nephrons.

The choice of pharmaceutical prophylaxis depends on the patient's risk of TLS. For intermediate-risk patients, allopurinol, typically 300mg daily for 7 days, is sufficient. In most high-risk adults, rasburicase should be used for prophylaxis at a single dose of 3mg, although careful monitoring is needed to assess any need for re-dosing. Rasburicase is a recombinant urate oxidase that can help convert uric acid to allantoin, which is more readily excreted. Rasburicase should not be used in patients with glucose-6-phosphate dehydrogenase deficiency and it is not advisable to use allopurinol and rasburicase together. This is because allopurinol is a xanthine oxidase inhibitor and works upstream of rasburicase to prevent uric acid production (Figure 7.2).

Treatment

Allopurinol is not the drug of choice for treating TLS. Instead, rasburicase, 0.2mg/kg/day, should be used; the treatment duration is determined by the clinical response.

TLS is primarily an issue in patients with acute leukaemias, but also patients with CLL receiving the BCL2 inhibitor venetoclax; initial use of this agent requires careful monitoring of the patient to prevent TLS.

Tumour lysis syndrome (cont.)

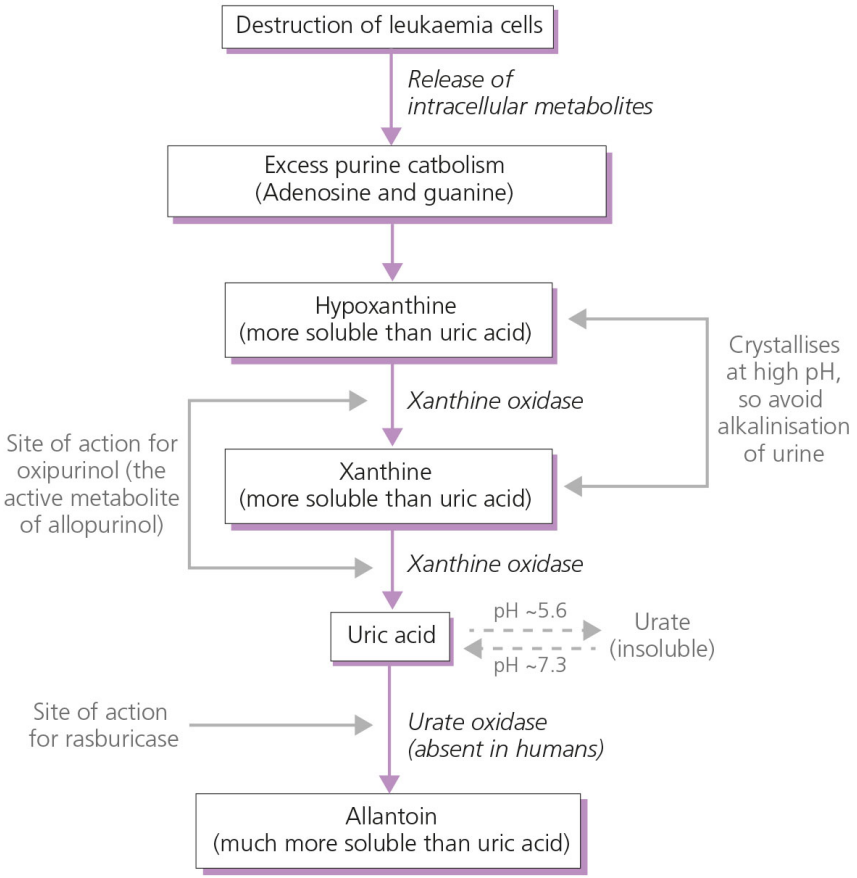

Figure 7.2 Sites of action of allopurinol and rasburicase. Rasburicase is a recombinant urate oxidase that helps to convert uric acid to allantoin. Allopurinol is a xanthine oxidase inhibitor that works upstream of rasburicase to prevent the production of uric acid. For this reason, it is not advisable to use allopurinol and rasburicase together.

Hyperleucocytosis and leucostasis

Hyperleucocytosis

Hyperleucocytosis – a marked elevation in leukaemic cells in the peripheral blood – is a frequent finding in patients with chronic and acute leukaemias. However, patients' ability to tolerate different WBC counts depends on the underlying type of leukaemia; for example, patients with CLL may tolerate a far higher WBC count than those with AML. In AML, hyperleucocytosis is arbitrarily defined as leukaemia blood cell counts greater than 100 109/L; and it is more common in patients with monocytic subtypes.

Leucostasis

Leucostasis is a medical emergency. It is more commonly seen in patients with AML, but symptomatic leucostasis may also be associated with a blast crisis in CML. Leucostasis occurs when WBC plugs form in very small blood vessels, potentially reducing the flow in the capillary beds and producing symptoms related to the affected organ. Pulmonary and neurological symptoms are most common. In some patients, leucostasis may result in a painful priapism.

Treatment

The management of leucostasis depends on whether the patient is symptomatic: patients may be hypoxic from pulmonary haemorrhage or confused from cerebral leucostasis. It may be difficult to exclude concomitant illnesses, such as pneumonia, that could also explain the clinical findings. Fundoscopy may identify retinal haemorrhages and engorgement of retinal vasculature.

A rapid reduction in WBC can be achieved by leukapheresis. However, concomitant chemotherapy is required to maintain depletion of the leukaemic cells, especially in patients with acute leukaemias in whom the blasts reaccumulate in a short time.

Differentiation syndrome

The use of ATRA and arsenic trioxide in the treatment of APML is associated with the development of differentiation syndrome. This potentially severe complication can affect approximately 25% of patients during the induction phase of treatment. Although the pathogenesis of differentiation syndrome has not yet been fully elucidated, it appears that ATRA activates a cascade of mechanisms that lead to an inflammatory response, with damage to the endothelium and migration of leucocytes into the surrounding tissue.

Differentiation syndrome is characterised by fever and features of cardiac failure, including dyspnoea, weight gain, peripheral oedema, and pulmonary infiltrates; it may also result in renal failure. Hyperleucocytosis may also be present. In severe cases, patients may require organ support in an intensive care setting.

It is important to be vigilant for differentiation syndrome because it is easily confused with concurrent illnesses such as infections.

Management of differentiation syndrome centres on intravenous dexamethasone, 10mg twice daily, until the syndrome settles. Although there is little evidence to support prophylactic corticosteroid treatment, it is commonly applied, especially in patients at high risk of differentiation syndrome. Treatment with ATRA or arsenic trioxide is usually continued unless the syndrome is particularly severe (for example, if the patient requires organ support), in which case treatment may be temporarily suspended while the syndrome is resolved.

Asparaginase-related thromboses in ALL

L-asparaginase is a vital component of paediatric and adult treatment protocols for ALL and has been part of the encouraging improvements in outcomes for patients with this leukaemia. The increased incidence of thromboses in patients with ALL (5% in children and higher in adults) is likely to be linked to the use of L-asparaginase, as thromboses are not as strongly associated with regimens that do not contain this agent. Thromboses most frequently occur in the venous system, including critical sites such as the cerebral venous sinuses and pulmonary vessels.

The mechanism of action underlying this increase in thromboses is multifactorial, including disruption of natural anticoagulants and activation of the coagulation cascade. L-asparaginase is particularly associated with a decrease in antithrombin, a natural anticoagulant that inhibits activated coagulation factors. Given the resultant prothrombotic state, which is worse during the initial stages of treatment, placement of central venous catheters should be avoided during induction treatment, as these may be a source of thromboses.

The management of thromboses is predominantly based on the use of low-molecular weight heparin (LMWH). However, as the anticoagulant mechanism of LMWH is dependent on antithrombin, the levels of which are affected by L-asparaginase, some clinicians also advocate the use of antithrombin infusions or other replacement products.

Key points – emergencies in leukaemia

- Sepsis should be treated immediately with broad-spectrum antibiotics, and intravenous fluids and oxygen as needed.
- The high risk of bleeding in uncontrolled APML represents a medical emergency. To prevent coagulopathy, antileukaemic therapy should be initiated as soon as possible, alongside meticulous supportive care.
- TLS may arise spontaneously but is more frequent in the early days of chemotherapy, when massive numbers of tumour cells are being destroyed.
- All patients at risk of TLS should be given intravenous fluids to maintain good diuresis.
- Both allopurinol and rasburicase can be used as prophylaxis in TLS depending on the patient's risk level. However, they should not be used together.
- Hyperleucocytosis is a frequent finding in both chronic and acute leukaemias, but leucostasis tends to be more common in patients with AML. Rapid reductions in WBCs can be achieved with leukapheresis, but concomitant chemotherapy is needed to maintain leucodepletion.
- Treatment with ATRA and arsenic trioxide has led to impressive improvements in survival rates in patients with APML. Still, their use may be associated with the development of differentiation syndrome. This can be managed with intravenous dexamethasone, 10mg twice daily.
- An increased incidence of thromboses in patients with ALL is probably linked to treatment with regimens containing L-asparaginase. To help reduce the incidence of thromboses, placement of central venous catheters should be avoided during the induction phase of treatment with these regimens.

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemiacare.org.uk

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Leukaemia Care is registered as a charity in England and Wales (no.1183890) and Scotland (no. SC049802).
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