Haematological problems in the intensive care unit

Katherine L McDowall
Katrina Parsons
Gillian A Horne

Abstract

Patients admitted to the intensive care unit can be affected by a range of haematological problems, either as a consequence of primary haematological disease or, more commonly, with haematological problems arising as a consequence of other disease processes. The haematological malignancies are individually relatively rare conditions, but collectively account for a significant proportion of cancer diagnoses. This group of conditions may cause patients to become critically ill and require intensive care support for a number of reasons.

Keywords Chemotherapy-induced febrile neutropenia; haematologic neoplasms; intensive care units; T-cell antigen receptor; tumour lysis syndrome

Royal College of Anaesthetists CPD Matrix: 2A12, 2C01, 2C03, 2C04

Learning objectives

After reading this article, you should be able to:

- outline common presentations of haematological malignancies to ICU
- describe some of the complications of the treatment of haematological malignancies which are of relevance to ICU and anaesthetic practice
- discuss the management of the above conditions in ICU

Non-malignant haematological problems

Nedelkovic and Davis[1] reviewed a number of predominantly non-malignant haematological conditions affecting ICU patients, including anaemia, massive transfusion, coagulopathy, heparin resistance and heparin-induced thrombocytopaenia in this journal in 2015. There has been relatively little change in how these conditions are managed in the intervening period. This article will therefore focus primarily on the problems that may cause patients suffering from haematological malignancies to present to ICU.

Haematological malignancies

Haematological malignancies are classified according to the cell lineage from which they arise. The various haematological malignancies differ in the rapidity with which the disease progresses and are described as acute or chronic, or in the case of the lymphomas, as low grade or high grade. A simplified classification is shown in Figure 1.

Katherine L McDowall *MA MRCP FRCA FFCIM is a Consultant Anaesthetist and Intensivist at the Queen Elizabeth University Hospital, Glasgow, UK. Conflicts of interest: none.*

Katrina Parsons *MRCP is a specialty trainee in Haematology at the Queen Elizabeth University Hospital, Glasgow, UK. Conflicts of interest: none.*

Gillian A Horne *PhD MRes MRCP is a clinical lecturer in Haematology at the Queen Elizabeth University Hospital, Glasgow, UK. Conflicts of interest: none.*

In the past, the admission of patients with haematological malignancy to ICU was discouraged on grounds of futility, but more recent data suggest this position is no longer tenable for the majority of patients.[2] Guidelines published in 2015 by the British Committee for Standards in Haematology in co-operation with the Intensive Care Society[3] recommend a trial of ICU for most patients, except competent adults who refuse and those who are suffering from a terminal disease process.

Nature of ICU presentations

Patients suffering from haematological malignancy may present to the ICU for a number of reasons, which may be due to the disease itself, as a consequence of the treatment required, or due to unrelated problems. Table 1 outlines some of the haematological manifestations of these conditions along with some of the important differential diagnoses. Table 2 describes some of the ways in which haematological malignancies, or the treatment thereof, can affect different organ systems and potentially lead to critical care admission.

There are a few specific complications of these diseases that merit separate consideration, either because they are common, or because they have significant implications for treatment. These will be considered in greater depth.

Neutropenic sepsis

Neutropenic sepsis can complicate treatment with cytotoxic agents. Neutropenic sepsis should be diagnosed in patients having anticancer treatment who have a neutrophil count of 0.5 $\times 10^9$/l, or lower and who have either a temperature higher than 38°C or other signs or symptoms consistent with sepsis.[4]

Patients may present with features of sepsis in the absence of localizing signs. Patients should have peripheral cultures taken as well as from any central line that is present. Other suspected sites of infection should be cultured. Sites of infection include skin, chest, blood stream, urinary and intestinal tract, other sites that may be overlooked include the mouth and sinuses. Patients should be treated empirically with broad-spectrum antibiotics. The initial recommendation from the National Institute of Health and Care Excellence (NICE) is to use piperacillin and tazobactam, unless the patient is allergic to penicillin or local guidelines recommend alternative agents. Other agents can be added if there are patient specific or local microbiological indications. Consideration should be given to adding in other agents to cover

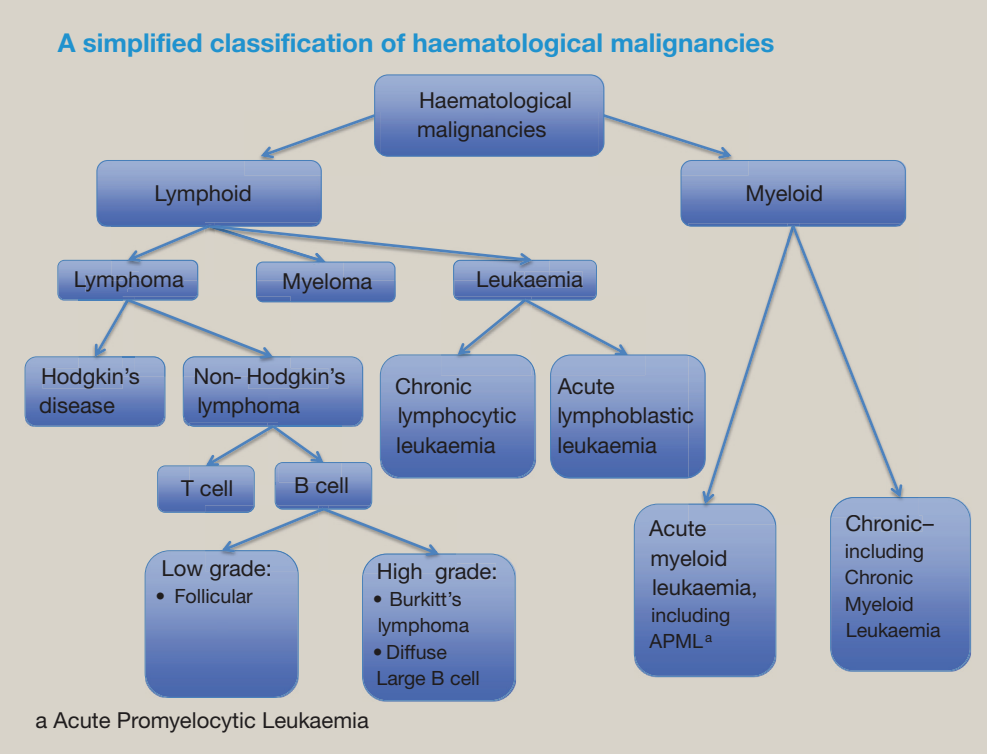

Figure 1

opportunistic infections, such as fungi, in patients who are failing to improve on conventional antibacterial agents. Granulocyte colony stimulating factor may be used to aid neutrophil count recovery in patients who are critically ill. This should be done after discussion with the haematology team. Strict infection control procedures are important and these patients should be reverse barrier nursed.

Patients may have other cytopaenias and this combined with the increased infection risk should be considered when undertaking invasive procedures. Patients may also require transfusion of red cells and platelets. A usual target for platelet counts would be:[5]

- $>10 \times 10^9$/l if no longer septic
- $>20 \times 10^9$/l in septic patients, as there is an additional risk of bleeding
- $>20 \times 10^9$/l for central line placement in experienced hands under ultra-sound guidance
- $>50 \times 10^9$/l in patients undergoing more invasive procedures, or who are bleeding
- $>100 \times 10^9$/l if the patient requires an invasive procedure involving high risk sites such as the central nervous system.

Following white cell count recovery there is a risk of deterioration, perhaps from an immune reconstitution syndrome.

Tumour lysis syndrome

When patients first present they may have a high tumour burden. Treatment can result in tumour lysis syndrome (TLS). TLS can also occur spontaneously in conditions such as Burkitt's lymphoma with a particularly rapid cell turnover. It can cause rapid development of life-threatening hyperkalaemia as intracellular contents are released into the circulation. Hypocalcaemia, hyperphosphataemia and hyperuracaemia from the release and breakdown of nucleic acids are other features. At-risk patients should receive prophylaxis. This would usually be in the form of allopurinol, or rasburicase for those at greatest risk. The choice and dose of agent should be discussed with haematology. These patients will require frequent monitoring of electrolytes following the initiation of chemotherapy. If severe TLS does develop, renal replacement therapy may be indicated in addition to treatment with rasburicase.[6]

Acute promyelocytic leukaemia

Acute promyelocytic leukaemia (APML) is a clinically and biologically distinct form of acute myeloid leukaemia characterized by the presence of genetic translocation involving the retinoic acid receptor alpha (RARA) gene. Treated, APML has the best prognosis of all AML subtypes, but presentation with life-threatening coagulopathy leads to a high mortality before the diagnosis is made and during initial treatment. For these reasons early recognition, emergency instigation of treatment as soon as APML is suspected and close monitoring during treatment is of utmost importance in order to prevent deaths in this highly treatable disease.

Presenting features

APML typically presents with the complications of pancytopenia and/or haemorrhage. The coagulation screen may be markedly abnormal with prolonged PT, APTT and low fibrinogen; D-dimers will be very high. As soon as APML is suspected, treatment should be commenced with all-trans retinoic acid (ATRA) pending confirmation of the diagnosis.

Haematological manifestations of haematological malignancies

Haematological manifestations	Presenting features	Causes
Cytopaenias	**Neutropaenia** Asymptomatic Fever Sepsis	**Impaired production** • Leukaemia • bone marrow failure syndromes • Cytotoxic Chemotherapy • Radiotherapy • Nutritional deficiencies
	Thrombocytopaenia Asymptomatic Petechiae/purpura Bruising Bleeding	**Increased destruction** • Autoimmune conditions • Drug related In the cases of thrombocytopenia and anaemia: • MAHA[a] including DIC[b], HUS[c], TTP[d] • Bleeding
	Anaemia Asymptomatic Tiredness Shortness of breath Dizziness	
Coagulopathy	Asymptomatic Bruising Bleeding	**Impaired production of clotting factors** • Malnutrition • Liver dysfunction • Drugs • Congenital/acquired factor deficiency
		Increased consumption • APML • Sepsis • Massive Haemorrhage

[a] Microangiopathic haemolytic anaemia.
[b] Disseminated Intravascular Coagulation.
[c] Haemolytic Uraemic Syndrome.
[d] Thrombotic Thrombocytopaenic Purpura.

Table 1

Coagulopathy

The coagulopathy of APML is unique, resulting from both disseminated intravascular coagulation (DIC) and primary hyperfibrinolysis. Untreated, it may lead to rapid death from pulmonary or intracranial haemorrhage. Even in patients who are diagnosed promptly and commenced on ATRA, the risk of haemorrhage is significant. Along with the early initiation of ATRA the management of this coagulopathy requires close monitoring of the platelet count and coagulation screen; checking at least twice daily and transfusing platelets and cryoprecipitate respectively to maintain:

- platelets $>30 \times 10^9$
- fibrinogen $>1.5 g/l$[7]

Differentiation syndrome

Differentiation syndrome (DS) complicates ATRA and/or arsenic treatment in up to 25% of patients with APML. Release of cytokines from maturing myeloid cells leads to a systemic inflammatory response causing fever, pulmonary infiltrates, pulmonary and peripheral oedema, pleural and pericardial effusions and hypotension. The timing of onset is bimodal with peaks in the first and third weeks of treatment.[8] Evidence to guide the treatment of DS is lacking, however accepted international guidelines advocate early treatment as soon as the diagnosis is suspected with:

- 10 mg dexamethasone twice daily.
- Actively ruling out other conditions with similar presenting features, e.g. pneumonia, left ventricular failure, pulmonary haemorrhage.
- Supportive care with meticulous monitoring of renal function, with at least twelve hourly bloods, or more frequently as determined by previous results.
- Severe cases may require the temporary suspension of ATRA or arsenic therapy.

Haematopoietic stem cell transplantation (HSCT)

HSCT is currently used as a treatment for conditions that cannot be cured with standard chemotherapy or radiotherapy. The stem cells used can be autologous, which allows for larger doses of chemotherapy to be given than would otherwise be possible. It is also possible to use allogenic stem cells from a donor. Here the patient may receive conditioning treatment that removes their own immune system and allows the donor cells to repopulate it.

Non-haematological complications of haematological malignancies

Organ system affected	Causes
Cardiovascular	**Cardiac failure** Anthracycline chemotherapy Pericardial effusion Direct cardiac infiltration AL amyloid
	Dysrhythmias Electrolyte imbalances due to TLS[a]/diarrhoea/drugs such as liposomal amphotericin B/Foscarnet Direct medication effect: Ibrutinib
	Hypotension Sepsis Cytokine release syndrome
Respiratory	**Infective complications of immunocompromise** Pneumonia Viral pneumonitis
	Drug induced pneumonitis/fibrosis Bleomycin Methotrexate Cyclophosphamide
	Graft versus host disease (GVHD) Pneumonitis
	Mechanical complications Mass effect from lymphoma (Potential airway compression at multiple levels)
Neurological	Direct central nervous system involvement Hyperviscosity syndromes High white cell counts – leukostasis in CML[b] High paraproteins – Waldenstrom's Macroglobulinaemia, multiple myeloma. Medication including: Ifosfamide, PD1[c] blockers CAR-T[d] cells (CRES)[e] Intracranial haemorrhage due to low platelets/coagulopathy
GI tract	**Mechanical complications - obstruction/perforation** Lymphoma
	Upper GI symptoms –Mucositis/nausea/vomiting Chemotherapy – especially Methotrexate, melphalan GVHD
	Lower GI symptoms – diarrhoea Neutropenic enterocolitis GVHD Infective colitis

Table 2 (*continued*)

Organ system affected	Causes
Hepatic	Infiltration Medication, e.g. asparaginase GVHD VOD[f]
Renal Impairment	Tumour lysis syndrome Myeloma Ciclosporin Platinum chemotherapy

[a] Tumour lysis syndrome.
[b] Chronic myeloid leukaemia.
[c] Programmed cell death protein 1.
[d] Chimeric antigen receptor T cells.
[e] CAR-T related encephalopathic state.
[f] Veno-occlusive disease.

Table 2

The donor cells can then assist in controlling any recurrent tumour cells (graft versus disease effect). Patients receiving this form of treatment are at high risk of developing complications which require ICU admission. There are some regimes which aim to use non-myeloablative chemotherapy in an attempt to reduce toxicity.

Graft versus host disease (GVHD)

GVHD is a condition which arises in patients who have undergone allogenic HSCT. The donor cells which are immunocompetent, target antigens on the host cells and cause significant inflammation. It may present acutely or chronically. In its chronic form, if severe, it is associated with significantly increased mortality and if refractory to treatment, critical care admission might not be appropriate.

Mechanical complications

Lymphomas and, to a lesser extent, myeloma may present with a range of mechanical complications raging from obstruction of various organ systems and perforated viscera. Although spinal cord compression is a feared complication, it is not one that would usually leads to ICU admission, unless it occurs in conjunction with other features.

Lymphoma may cause airway obstruction at a number of levels and careful assessment to the position of any masses is vital in order to plan appropriately. Masses causing subglottic airway obstruction are a particular concern, as is superior vena cava syndrome (SVCS). SVCS arises because of compression, or thrombosis of the superior vena cava. It can be classified into grades 1–5 (mild to fatal). In the less severe end of the spectrum, most evidence suggests trying to elucidate the aetiology and obtain a tissue diagnosis prior to initiating treatment. In severe cases, it is necessary to institute treatment prior to obtaining a histological diagnosis. For suspected lymphoma this would involve steroids and prophylaxis against TLS.

Grade 4 SCVS occurs when there is stridor or cerebral oedema. It is rare, but constitutes a true medical emergency, the management of which is controversial. Guidelines recommend immediate tracheal intubation for airway protection.[9] However, this is a particularly challenging as the situation can be worsened following the induction of anaesthesia with potentially adverse outcomes due to loss of venous return, or loss of the airway. Some authorities therefore recommend the institution of cardiopulmonary bypass prior to the induction of anaesthesia. Other options include emergency stenting of the SVC. Which of these options is employed may ultimately be determined by the facilities available locally and the specifics of the individual case.

Future developments

Given the toxicities associated with some treatments such as allogenic HSCT, there has been a hunt for novel approaches.

Chimeric antigen receptor T cells (CAR-T) permit a targeted therapeutic approach by utilizing genetically modified T cells that express a receptor to specifically target surface antigens on malignant cells. CAR-T therapy has produced extraordinary results in relapsed/refractory B-cell acute lymphoblastic leukaemia and lymphoma, with complete remission rates ranging from 70 to 94%.[10–12] Nevertheless, its delivery is not without toxicity. Frequently occurring toxicities that lead to critical care admission include cytokine release syndrome (CRS), CAR-T-related encephalopathic state (CRES) and more rarely, CRS evolving into haemophagocytic lymphohistiocytosis. Less severe toxicities, such as hypersensitivity and long-term toxicities, such as B-cell aplasia, have been reported.

CRS is the most frequently occurring toxicity of immune-modulatory therapy, and occurs from the release of pro-inflammatory cytokines, including IL6, interferon gamma, and IL-2. Clinical symptoms are characterized by pyrexia (sometimes greater than 40°C), vascular leak and organ dysfunction. Occasionally, there can be associated neurological manifestations,

including headache, confusion, or altered mental state. Timing and severity depend on the extent of immune activation and cytokine release, but in most cases, CRS occurs from 3 days to 2 weeks post infusion. Presentation can be difficult to distinguish from infection and sepsis, and it is important to recognize this as part of a differential diagnosis. The diagnosis, itself, is based on clinical acumen, with no specific peripheral blood test to make the diagnosis. CRP levels coincide with IL6 release and may be useful in tracking the clinical course.

As clinical symptoms in CRS are intrinsic to the biological process of CAR-T therapy, the decision to initiate treatment to suppress it should be carefully considered. Grading severity is important to help make this decision. Definitive treatment options include, the monoclonal antibody against IL-6, tocilizumab and steroids. Tocilizumab has been shown to be efficacious in severe or life-threatening CRS at a dose of 4mg/kg IV in adults, and 8mg/kg IV in children.[13] In all cases of suspected CRS, the decision to treat with tocilizumab or steroids should be discussed with the lead clinician from the base team in view of the potential to reduce the efficacy of the immune-modulatory therapy itself.

Patients who have received CAR-T therapy are likely to become more commonly encountered within a critical care setting. Balancing life-threatening toxicity while maintaining beneficial anti-tumour effect is imperative. A multidisciplinary team approach should be adopted between the base team (haematology or oncology), immunology, neurology, and critical care to ensure appropriate management. ◆

REFERENCES

1 Nedelkovic M, Davis AK. Haematological problems in intensive care. *Anaesth Intensive Care Med*, 2015; https://doi.org/10.1016/j.mpaic.2015.09.009. Published on-line October 30, 2015.

2 McDowall KL, Hart AJ, Cadamy AJ. The outcomes of adult patients requiring admission to the Intensive Care Unit. *J Intensive Care Soc* 2011; **12:** 112–25.

3 Wise MP, Barnes RA, Baudouin SV, et al. Guidelines on the management and admission to intensive care of critically ill adult patients with haematological malignancy in the UK. *Br J Haematol* 2015; **171:** 179–88. https://doi.org/10.1111/bjh.13594.

4 NICE Guidance. Neutropenic sepsis: prevention and management in people with cancer. 2012 (Accessed 31 May 2018), https://www.nice.org.uk/guidance/cg151/evidence/full-guideline-pdf-188303581.

5 Estcourt LJ, Birchall J, Allard S, et al. Guidelines for the use of platelet transfusions. *Br J Haematol* 2017; **176:** 365–94. https://doi.org/10.1111/bjh.14423, http://orcid.org/0000-0003-4309-9162. NHSBT and Radcliffe Department of Medicine, University of Oxford, UK.

6 Jones GL, Will A, Jackson GH, et al. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol* 2015; **169:** 661–71. https://doi.org/10.1111/bjh.13403.

7 Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. *Blood* 2009; **114:** 5126–35. https://doi.org/10.1182/blood-2009-07-216457.

8 Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood* 2014; **123:** 2777–82. https://doi.org/10.1182/blood-2013-10-512640.

9 Weiss KS, Van Zuuren EJ, Loughlin KR, eds. Superior vena cava syndrome 2015 (Accessed 31 May 2018), http://www.dynamed.com.knowledge.idm.oclc.org/topics/dmp~AN~T113759/Superior-vena-cava-syndrome.

10 Maude SL, Laetch TW, Buechener J, Rives S. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *NEJM* 2018; **378:** 439–48.

11 Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor –modified T cells for acute lymphoid leukemia. *NEJM* 2013; **368:** 1509–18.

12 Locke FL, Neelapu SS, Barlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. *Mol Ther* 2017; **25:** 285–95.

13 Lee DW, Gardner R, Porter DL, et al. How I Treat: current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014; **124:** 188–96.