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REVIEW

Therapeutics for paediatric oncological emergencies

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Abstract

Background: With advancements in the field of oncology, cancer survival rates have improved dramatically but modern cancer treatments also come with an increasing number of disease and treatment-associated complications. This article provides an updated narrative review on the pathophysiology, clinical presentations and latest management strategies for common paediatric oncological emergencies.

Methods: An extensive PubMed® search of all human studies in the English literature was performed in Clinical Queries for different oncology syndromes and conditions using the following Medical Subject Headings: "tumour lysis syndrome", "hyperleukocytosis", "disseminated intravascular coagulation", "superior mediastinal syndrome", "superior vena cava syndrome", "sepsis", "severe inflammatory response syndrome", "acute respiratory distress syndrome", "posterior reversible encephalopathy syndrome" and "reversible posterior leukoencephalopathy syndrome". Categories were limited to clinical trials and reviews for ages from birth to 18 years.

Results: The general description, presentation and management of these oncologic emergencies are systematically described. Early recognition along with prompt and proactive treatment can reduce the chances of potential complications and improve the clinical outcomes, thereby improving not only survival rates in oncology patients but also their clinical outcomes and quality of life.

Conclusions: Oncologic emergencies are associated with significant mortality and morbidity. Healthcare professionals involved with the care of oncology patients must be vigilant of these emergencies.

Keywords: acute respiratory distress syndrome (ARDS), Cancer, critical care, disseminated intravascular coagulation, hyperleukocytosis, oncologic emergency, paediatrics, posterior reversible encephalopathy syndrome (PRES), sepsis, superior mediastinal syndrome, therapeutics, treatment, tumour lysis syndrome.

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Introduction

Paediatric oncology is a complicated multidisciplinary subspecialty. Healthcare professionals should be aware of the many and often serious syndromes associated with the management of paediatric oncologic conditions to prevent their occurrence and mitigate potentially severe consequences through proactive interventions. With advancements in the field of oncology, cancer survival rates have improved dramatically in recent years and more than 80% of children with cancer can now be expected to survive for 5 years or more.[1,2] On the other hand, longer survival comes at the expense of an increasing number of disease and treatment-associated complications, as modern cancer treatments can have potentially life-threatening side effects.[3] Early recognition and prompt treatment of these oncologic emergencies can considerably reduce the chances of potential complications and improve clinical outcomes. The objective of this review is to examine the body of literature on the pathophysiology, clinical presentation and the most up-to-date management strategies for oncological emergencies. Common oncological emergencies are summarized in Table 1.

Table 1. Common oncological emergencies.

System	Oncological emergencies
Metabolic	Tumour lysis syndrome[a] Hypocalcaemia Hypercalcaemia Hypoglycaemia Hyperkalaemia Hyperphosphataemia
Haematological	Anaemia Leukopenia Hyperleukocytosis[a] Hyperviscosity syndrome Disseminated intravascular coagulation[a] Hemophagocytic lymphohistiocytosis
Cardiovascular	Superior vena cava syndrome[a] Pericardial effusion/pericardial tamponade
Respiratory	Superior mediastinal syndrome[a] Acute respiratory distress syndrome[a] Pulmonary embolism
Neurological	Raised intracranial pressure and brain herniation Posterior reversible encephalopathy syndrome[a] Spinal cord compression Brain metastasis
Infection	Sepsis[a] Febrile neutropenia[a]
Haematopoietic cell transplantation related	Graft *versus* host disease Sinusoidal obstruction syndrome Thrombotic microangiopathy

[a]Condition described in this narrative review.

Methods

An extensive PubMed search of all human studies in the English literature was performed in Clinical Queries in November 2020 for different oncology syndromes and conditions using the following Medical Subject Headings: "tumour lysis syndrome", "hyperleukocytosis", "disseminated intravascular coagulation", "superior mediastinal syndrome", "superior vena cava syndrome", "sepsis", "severe inflammatory response syndrome", "acute respiratory distress syndrome", "posterior reversible encephalopathy syndrome" and "reversible posterior leukoencephalopathy syndrome". Categories were limited to clinical trials and reviews for ages from birth to 18 years. The retrieved articles form the basis of this literature review, although the full extent of the literature review is not limited to this search.

Review

Oncologic emergencies

Tumour lysis syndrome

Tumour lysis syndrome (TLS) is a life-threatening oncological emergency resulting from the rapid lysis of tumour cells and abrupt release of their intracellular content into circulation.[4–6] The prevalence of TLS varies amongst different malignancies and definitions and is estimated to be between 4% and 42%, whilst the related mortality is reported to be up to 21% in paediatric patients with haematological malignancies.[6–9] TLS usually occurs after cytotoxic therapy, most commonly in patients with haematological malignancies, particularly acute lymphoblastic leukaemia and Burkitt lymphomas in children.[10] The occurrence of TLS in patients with solid tumours is less frequent. Other tumour-related risk factors include high tumour load, high proliferative rates, high tumour chemosensitivity and increased lactate dehydrogenase levels.[11–15] Cairo and Bishop is the most common classification system for TLS. TLS can also be classified into laboratory TLS and clinical TLS.[7,11] Laboratory TLS is defined as the presence of two or more blood abnormalities (uric acid, potassium, phosphorus, calcium) within 3 days before or 7 days after the initiation of chemotherapy, whilst clinical TLS is defined as the presence of laboratory TLS with one or more of the following: cardiac arrhythmia or sudden death and seizure.[11]

The timing of TLS presentation is usually 12–72 hours after the initiation of cytotoxic therapy.[11,16,17] Spontaneous TLS without any obvious trigger is rare but has been increasingly documented in Burkitt's lymphoma.[18–20] The clinical

manifestations of TLS include nausea, vomiting, diarrhoea, muscle cramps, paraesthesia, oedema, congestive heart failure, cardiac dysrhythmias, seizure and sudden death.[9,11] The release of intracellular metabolites can overwhelm the normal homeostatic mechanism and can cause hyperkalaemia, hyperphosphatemia, hypocalcaemia, hyperuricemia and acute renal failure.[7,11]

Management

The key to the management of TLS includes close monitoring and prophylactic strategies for at-risk patients as well as a high index of suspicion and early recognition and treatment of metabolic and renal complications.[11] A risk assessment of TLS based on the malignant disease type should be performed. In general, the risk of TLS for most solid tumours is low, except for bulky solid tumours. Solid tumours, which are sensitive to chemotherapy, including neuroblastoma and germ-cell tumour, are classified as intermittent risk.[21] The risk assessment of acute leukaemia is based on white blood cell counts and LDH levels, where high values (≥100 × 10^9/L and ≥2 × upper limit of normal, respectively) are considered high risk for TLS. Burkitt lymphoma/leukaemia is always classified as high risk for TLS.[21] The risk of TLS is also higher in patients with pre-existing renal impairment or disease involving the kidney at diagnosis.[21]

For at-risk cases, TLS parameters, including potassium, phosphate, uric acid, calcium, creatinine and LDH levels, should be monitored every 4–6 hours and patients with established TLS should ideally be monitored in high dependency or intensive care settings.[7] Fluid balance should be monitored with urine output as TLS could lead to oliguria by obstructive uropathy and hyperhydration can lead to fluid overload in patients at risk.[6,22,23] Preventive measures include aggressive hydration (3 L/m^2/day), diuresis to maintain a urine output of ≥100 mL/m^2/hour (3 mL/kg/hour if ≤10 kg) and antihyperuricaemic agents.[11] Commonly used antihyperuricaemic agents are allopurinol and rasburicase. These agents act on the purine catabolism pathway to reduce the uric acid level in the blood. Allopurinol, a xanthine analogue, decreases the production of uric acid by inhibiting the action of xanthine oxidase; however, as it does not reduce serum uric acid levels, it is used in prophylaxis in patients with low to intermittent risk of developing TLS only.[6] For patients with an intermittent to high risk of TLS or with pre-existing hyperuricaemia, rasburicase, a recombinant urate oxidase, can be used.[6,21] Rasburicase can decrease uric acid rapidly by converting it into allantoin, which is more soluble in water than uric acid, and the suggested dose by the manufacturer is 0.2 mg/kg/dose daily for up to 5 days.[24] Rasburicase is generally well tolerated but, as the serious adverse events include haemolytic anaemia and methaemoglobinaemia, it is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.[25]

Generally, the management approach can be guided according to the risk stratification: (1) low-risk patients should be closely monitored and hydration might be sufficient; (2) intermediate-risk patients should initiate allopurinol in addition to hydration; however, if hyperuricaemia develops, rasburicase therapy should be commenced; and (3) high-risk patients should undergo hydration plus the initiation of rasburicase therapy.[7] Other treatment strategies include correcting electrolyte abnormalities and the use of renal replacement therapy in refractory electrolyte abnormalities and acute renal failure. Urine alkalinization is currently not recommended as a treatment for TLS and should only be considered in patients with metabolic acidosis.[7,26]

Hyperleukocytosis

Hyperleukocytosis is defined as a peripheral white blood cell count >100 × 10^9/L and it is a medical emergency.[27] Hyperleukocytosis is associated with haematological malignancies, in particular T cell acute lymphoblastic leukaemia (ALL), infant ALL and acute myeloblastic leukaemia (AML).[28] As the size of myeloblasts in AML is twice that of lymphoblasts in ALL, patient with AML and hyperleukocytosis have a high risk of early morbidity and mortality compared to patients with ALL.[29] The incidence at presentation ranges from 5% to 22% in AML, in nearly all patients in chronic myeloid leukaemia and 9–13% in ALL.[30,31]

Hyperleukocytosis leads to an increased whole blood viscosity, causing aggregation of blasts cells in the microvasculature, which can lead to leukostasis and microvascular occlusion.[30] The rapid breakdown of leukocytes will result in tumour lysis syndrome and the release of tissue factor leads to coagulopathy. Hyperleukocytosis and leukostasis symptoms include neurological symptoms (headache, seizures, dural sinus thrombosis), visual field changes (cortical infarction, retinopathy), pneumonitits, respiratory distress, myocardial ischaemia, disseminated intravascular coagulopathy and multiorgan failure.[31,32]

Management

The principle in the management of hyperleukocytosis includes hyperhydration to reduce whole blood viscosity, the prevention of tumour lysis syndrome, correcting metabolic abnormalities and early chemotherapy.[28] Leukopheresis decreases the total leukocyte count by 20–50% and can be considered in symptomatic patients.[28] However, the use of leukopheresis for leukoreduction in leukaemic patients is controversial and there are no guidelines for paediatric patients. Due to technical difficulties in small children, the potential of leukapheresis-related complications (up to 85%) and the lack of long-term survival benefit, routine leukopheresis is not recommended.[31,33] Blood transfusion should be avoided in hemodynamically stable patients as it increases blood viscosity. Platelets can be transfused liberally to maintain 50 × 10^9/L to prevent bleeding and CNS complications.[32]

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is an acquired condition, triggered by the activation of the coagulation cascade, leading to the consumption of platelets and clotting

factors followed by the intravascular deposition of fibrins.[34–36] This can result in severe bleeding, thrombosis of small to midsize vessels, and ultimately multiorgan dysfunction and failure.[36] Amongst the various aetiologies of DIC, the most important are sepsis and disseminated malignancies. In oncology patients, DIC can also be triggered by additional causes, including TLS, leukocytosis and hemophagocytic syndromes.[37] It is estimated that 10–15% of patients with solid tumours and 15% of acute leukaemia patients have some degree of DIC, in particular those with acute promyelocytic leukaemia.[34,36] A recent systemic review of DIC in children with cancer reported that the mortality varied from 6% to 73%, with deaths caused mainly by fetal haemorrhage and organ dysfunction.[37]

Some patients with oncology-associated DIC might be asymptomatic and only have laboratory evidence of DIC, whilst those in extreme cases might have uncontrolled haemorrhage or therapy-resistant thrombosis.[38] The clinical presentation of DIC can be classified into three distinct groups: (1) subclinical, where the effect of thrombin and plasmin generated can only be reflected in the laboratory markers, more likely in solid tumours; (2) hyperfibrinolysis, where the predominate clinical symptoms are bleeding, as the activation of the fibrinolytic system dominates, more likely in acute promyelocytic leukaemia; and (3) hypercoagulation, where thrombosis is the predominant clinical symptoms, caused by excess thrombin, more likely in pancreatic and lung adenocarcinoma.[38,39] Common clinical presentations include mucocutaneous haemorrhage, gastrointestinal haemorrhage, melena and haematuria. Less common presentations include haemothorax, sinus thrombosis and pulmonary embolus.[37] In terms of general indicators of DIC, the platelet count is usually low or there could be a sudden drop along with prolonged clotting times, the presence of fibrin-degradation products, and low plasma levels of coagulation inhibitors.[36] For patients at risk of developing oncology-related DIC, regular blood cell counts and coagulation screening should be performed and DIC should be considered in case of a sudden deterioration of laboratory parameters, for example, >30% drop in platelet count.[38] There are several objective scoring criteria to diagnose DIC, and the criteria from the International Society on Thrombosis and Haemostasis is one of them.[40] This consists of a five-step diagnostic algorithm to calculate the DIC score based on four laboratory tests (platelet count, fibrin markers, prothrombin time and fibrinogen level).[37,40,41]

Management

The main goal in the management of DIC is to treat the underlying cause. Appropriate treatment for the underlying cancer should be used to treat cancer-related DIC.[38] Acute promyelocytic leukaemia is one of the most common causes of cancer-related DIC in children, particularly at disease onset, due to procoagulant molecules expressed by leukaemic cells such as tissue factor and cysteine proteases.[37] All-transretinoic acid should be given as soon as acute promyelocytic leukaemia is suspected as it can downregulate the procoagulant activities of the promyelocytic blasts and endothelial cells, leading to rapid improvement in coagulopathies, and it has been associated with decreased rates of early haemorrhagic deaths.[42]

Another treatment is predominately supportive in nature with judicious use of blood products, including platelet, fibrinogen and cryoprecipitate. It is important to assess the thrombotic and bleeding risk of the cancer patient by reviewing the clinical and laboratory parameters of direct management, for example, an oncology patient presenting with an embolic event should be evaluated for subclinical or procoagulant DIC.[38] Blood product transfusion should only be reserved for active bleeding or in patients at risk of bleeding (e.g. requiring surgery or invasive procedures).[38,41] In patients with DIC and active bleeding, platelet transfusion should be given to maintain a platelet count of $>50\times10^9$/L and fresh frozen plasma (FFP) can be given too. Prothrombin complex concentrate can be given instead of FFP if the fluid overload is a concern. In patients with persistently low fibrinogen (below 1.5 g/L), a cryoprecipitate or fibrinogen concentrate can be given.[38] The aim is to stop or reduce clinically significant bleeding, rather than normalizing laboratory parameters.[43] Heparin only has a limited role in paediatric patients with DIC and is reserved for those with life-threatening or symptomatic thrombosis.[44] Tranexamic acid may be considered in therapy-resistant bleeding in hyperfibrinolytic DIC.[38]

Superior vena cava syndrome and superior mediastinal syndrome

Airway compression and superior vena cava (SVC) obstruction are the two features that form these syndromes. SVC syndrome is the compression or obstruction on major vessels, whilst superior mediastinal syndrome is the compression or obstruction of the SVC and airways. In children, superior mediastinal mass syndrome is more common as a mediastinal mass pathology that compresses the SVC will often result in airway compression due to a limited chest volume.[45] Children are especially prone to airway obstruction at an earlier stage due to the smaller airway diameter, in which a >30% decrease in the luminal area represents a grave risk for total airway obstruction.[46] The majority of the mediastinal masses in children are in the anterior mediastinum. Common underlying diagnosis of mediastinal masses in children are often attributed to lymphoma, followed by germ-cell tumours, neuroblastoma and thymoma.[47,48] Management is often challenging and these conditions are associated with high mortality rates (16.4–40%).[47,49]

Clinical presentation can be insidious as the growth rate of some of these masses are slow, with around 30% of childhood mediastinal mass cases presenting with non-specific symptoms.[50,51] The effects of a mediastinal mass on the respiratory system include obstructive physiology caused by direct compression on the airway and restrictive physiology, where the total lung capacity and functional residual capacity are restricted by the compression of the mass or pleural effusion. In addition, the effects on the cardiovascular

structures include direct mechanical compression to the SVC, the right and left ventricular outflow tracts, and pericardial effusion. High-risk symptoms for decompensation include cough, noisy breathing with stridor or wheeze, orthopnoea and syncope.[45,51–54] Clinical signs of cyanosis, upper body oedema, engorgement of veins and pulsus paradoxical changes in blood pressure might indicate significant mass effects on surrounding anatomical structures.[45,51–55]

Management

A multidisciplinary team discussion including at least an oncologist and intensivist should be initiated as soon as possible to discuss the management plan. Apart from chest X-ray, an echocardiogram and CT scan are also useful diagnostic tools to evaluate the degree of compression by the mediastinal mass on the surrounding structures. For children with significant mass effects, they should be managed in a high dependency or intensive care environment for close monitoring of potential airway obstruction and cardiovascular decompensation.

Children should be allowed to adopt the posture of comfort and a rescue position with the most ideal physiological parameters should be determined.[56] To reduce the mediastinal mass effect, the elevation of the head, lateral or prone position can be considered as these positions can decrease the effects of the mass on airway and vascular structures. Spontaneous breathing should be maintained, whilst positive pressure ventilation, sedation and neuromuscular blocking agents should be avoided. The latter may reduce the negative intrathoracic pressure which, in return, may result in cardiorespiratory collapse.[57] Fluid status should be optimized to maintain sufficient venous return and cardiac output. The patient should also be managed in a specialized oncology centre, ideally with cardiothoracic surgery capabilities to facilitate timely treatment of the malignancy. Depending on the presentation history and imaging findings, steroid therapy and radiotherapy can be considered to reduce the size of the tumour. Although controversial, steroids and hyperhydration might be considered in some cases prior to biopsy to minimize the cardiorespiratory morbidity.[57,58] Extracorporeal membrane oxygenation (ECMO) might be required as a supportive or rescue therapy during diagnostic and therapeutic management to support the patient haemodynamically.[59]

Acute respiratory distress syndrome

Acute respiratory failure is a leading cause of intensive care admissions amongst oncology patients and patients with malignancies are at a high risk of severe pulmonary complications that could lead to acute respiratory distress syndrome (ARDS).[60,61] Mortality amongst paediatric oncology patients with respiratory failure requiring ventilation is higher (30–84%), and more than 50% of patients who develop ARDS will not survive hospital discharge.[62–64] Invasive ventilation with systemic infection or haemopoietic cell transplant is associated with a poor prognosis.[65] For those who survive ARDS, they often have residual organ dysfunction and poor functional status, delaying subsequent cancer treatment.[64]

ARDS is characterized by tachypnoea, dyspnoea and hypoxemia, with chest radiograph showing bilateral infiltration. In oncology patients, pulmonary and extrapulmonary infections are the major cause (up to 90%) of ARDS and up to one-third of the underlying infections were due to opportunistic pathogens, including invasive aspergillosis and *Pneumocystis* pneumonia.[64,66] Diagnostic bronchopulmonary alveolar lavage (BAL) can be used to guide treatment, the diagnostic yield of BAL in immunocompromised children ranges from 28% to 68%.[67] The primary lung insult of ARDS includes lung injury following aspiration, toxicity from pneumotoxic drugs, radiation toxicity and post-thoracic surgical changes. Other aetiologies include reduced baseline lung function post-chemotherapy (e.g. bleomycin reducing the diffusing capacity of the lung for carbon monoxide), diffused alveolar haemorrhage, pulmonary leukostasis, transfusion-related acute lung injury, pancreatitis and sepsis.[64,68,69]

Management

Early supportive interventions and treatment of the underlying cause in patients with respiratory failure are associated with better outcomes.[68] A timely diagnosis with appropriate supportive management is required to maximize the prospects of survival and pre-emptive therapy against invasive fungal infections should be considered in high-risk patients. The main goals of management are to treat the underlying cause and to avoid secondary lung injury and extrapulmonary complications. Early non-invasive positive pressure ventilation, lung-protective ventilation strategies (moderately elevated PEEP, patient-specific tidal volume and permissive hypercapnia), the consideration of neuromuscular blockage to achieve effective mechanical ventilation, conservative fluid management and adequate nutrition are suggested by the latest paediatric ARDS guideline.[70] The use of inducible nitric oxide, high-frequency oscillatory ventilation, prone positioning and corticosteroids remain controversial.[70] The use of ECMO in patients with underlying malignancy and haematopoietic cell transplantation are considered as relative contraindications by most centres but recent literature and Extracorporeal Life Support Organization database reviews reported a reasonable survival rate (10–35%).[71,72] ECMO might be considered in carefully selected patients where the prognosis of the malignancy is an important factor, for example, haematopoietic cell transplantation patients with non-malignant disorders.[71,72] Mesenchymal stem cell therapy might be a potential therapeutic for ARDS; there are preclinical studies supporting the anti-inflammatory, antiapoptotic, antimicrobial and proangiogenic effects of mesenchymal stem cells to disrupt pulmonary endothelial and epithelial cell damage, which can potentially prevent lung and distal organ injury in patient with ARDS.[73]

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome, is rare but recognized as one of the most common neurological complications in paediatric oncology patients.[74] It has been reported in 0.3–3% of children with cancer.[31] It is a condition in which parts of the brain are affected by swelling, usually as a result of an underlying cause.[75,76] Common underlying causes include severe hypertension, renal dysfunction, severe infections, certain medications and selected autoimmune diseases. Steroids, immunosuppressive agents or cytotoxic agents are common triggers for PRES and they can also result in hypertension or renal dysfunction.[77,78] These complications are increasingly being recognized and reported, mainly in childhood leukaemic patients.[77,78]

Symptoms of PRES may include headache, changes in vision, seizures, confusion and weakness of one or more limbs. In a multicentre survey of 112 paediatric oncology patients with PRES, the majority of patients presented with clinically significant syndrome after a cycle of chemotherapy followed by haematopoietic cell transplantation.[74] The condition predominantly (though not exclusively) affects the posterior cerebral hemispheres, in particular the parieto-occipital regions. The diagnosis is usually made by MRI of the brain; classical imaging findings of vasogenic oedema within the posterior arterial watershed region suggest a reversible process, whereas cytotoxic oedema or other atypical findings may suggest a less favourable prognosis.[77]

Management

Symptoms of PRES should be promptly recognized and treated. Although PRES is reversible in most cases, it can be life-threatening and result in residual symptoms or permanent neurological damage if not promptly recognized and treated.[77] The treatment for PRES is supportive in nature and symptom directed and there are no uniform treatment guidelines. Trigger events and causative drugs should be removed or discontinued. Other supportive management includes sufficient hydration, maintaining arterial oxygenation, correction of hypoglycaemia, electrolyte disturbances and coagulopathy. Elevated blood pressure should lower gradually to premorbid levels; the initial drop for the first 6–8 hours should not be more than 25–50% of the original value, followed by a gradual reduction over 24–96 hours.[79,80] Intravenous nicardipine and labetalol are considered first-line therapies for the management of hypertensive crises in children.[80] Anticonvulsants might be required for seizure control and the duration of treatment varies from as soon as symptoms resolve to up to 2 years following PRES.[81] Complications, including seizures and hypertension, should ideally be managed in a high dependence or intensive care environment. PRES may be further complicated by intracranial haemorrhage but this is relatively rare.

Infection

Paediatric oncology patients are particularly at risk of sepsis or sepsis-related syndromes as a result of either the underlying disease or as a consequence of intensive treatment, including chemotherapy and immunosuppressants by way of neutropenia and immunosuppression. Febrile neutropenia is common in oncology patients, with up to 80% of patients receiving chemotherapy for haematological malignancies developing febrile neutropenia at least once during the course of treatment.[82] Oncology patients are 10 times more likely to acquire sepsis than patients who do not have cancer, and it is a major cause of morbidity and mortality in oncology patients.[83,84]

Most common bacterial pathogens are gram-positive bacteria (e.g. *Streptococci viridians* and *Staphylococcus aureus*), followed by gram-negative bacteria (e.g. *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*) and viruses.[85] Fungal infections account for 2–10% of initial microbiologically confirmed infections in febrile neutropenic patients with cancer; empirical antifungal therapy should be initiated in high-risk patients with prolonged (≥96 hours) febrile neutropenia and radiological imaging might be required to evaluate the source of invasive fungal disease.[86] Patients at high risk of invasive fungal disease are those with acute myeloid leukaemia, high-risk acute lymphoblastic leukaemia, relapsed acute leukaemia, those undergoing allogenic haemopoietic cell transplantation, those receiving high dose steroids and those with prolonged neutropenia.[87] Viral infections are common causes of infection in immunocompromised patients but the majority will only cause mild symptoms.[88] However, in patient undergoing haematopoietic cell transplantation, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, human herpesvirus-6, human herpesvirus-7 and polyomavirus (e.g. BK virus) have to be considered.[89] Paediatric oncology patients also have increased susceptibility to opportunistic infections, especially neutropenic and hematopoietic cell transplant recipients.[90,91]

Management

Oncology patients with febrile neutropenia should be started on empirical antibiotic therapy with broad coverage promptly to cover the most likely pathogens that may rapidly escalate to serious or life-threatening sepsis. It is also important to be aware that neutropenic patients with severe sepsis may not be febrile. The American Society of Clinical Oncology recommends the first-line treatment of either monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin or carbapenem.[87] For patients who are clinically unstable or are suspected of resistant infection, a second antimicrobial effective for the treatment of gram-negative bacteria or a glycopeptide should be added.[87] With the emergence of antibiotic-resistant pathogens (e.g. vancomycin-resistant *Enterococcus*, methicillin-resistant *Staphylococcus aureus*, multidrug resistant gram-negative bacteria, carbapenem-resistant *Enterobacteriaceae*), advanced antibiotics to cover

these organisms can be considered.[92,93] Throughout the course of treatment, the antibiotics regimen should be adjusted and tailored according to the potential source of infection, culture results and sensitivity. Apart from the early use of broad-spectrum appropriate antibiotics, it is also important to identify and remove the potential source of infection. Bloodstream infections in oncological patients are not uncommon and can be associated with the translocation of bacteria through mucositis and the presence of a central venous catheter. Central line-associated bloodstream infections are correlated with prolonged hospitalization, intensive care admissions and increased mortality in oncology patients; therefore, suspicions should be high and measures should be in place to reduce the risk.[92,94] In order to reduce this risk, regular education and training should be provided for all staff and parents caring for patients with a central line, including good hand hygiene, maximal barrier precautions, chlorhexidine skin antisepsis, regular assessment of central line and removing unnecessary catheters.[92,95]

Routine granulocyte colony-stimulating factor (G-CSF) in a patient with neutropenic sepsis is not recommended as there is insufficient evidence to determine whether G-CSF influences the overall mortality.[96] G-CSF can be considered in bacteraemia, fungemia, invasive bacterial tissue infiltration or invasive fungal infection, unresponsive to appropriate antimicrobial therapy.[97] The beneficial effects of intravenous immunoglobulin for sepsis are not proven and therefore not recommended.[98] Adjunctive hydrocortisone should always be considered in children receiving treatment with acute or chronic corticosteroids, congenital adrenal hyperplasia, hypothalamic–pituitary–adrenal axis disorders and multiple endocrinopathies.[99,100] As the evidence for improved outcomes with the use of corticosteroids is marginal, the latest version of the Paediatric Surviving Sepsis guidelines does not have specific recommendations about hydrocortisone use.[98]

As most oncology patients are immunocompromised, regular infection surveillance, pre-emptive therapy, prompt treatment and appropriate use of prophylactic antimicrobials should be considered as a preventive measure of infection, especially in haematopoietic cell transplant patients.

Conclusion

With advancements in the field of oncology, the number of oncology patients presenting with oncology emergencies and complications will certainly continue to increase. For further improvements in the survival rate and quality of life of affected patients, all efforts should be taken to reduce the risk of potential complications. The oncological emergencies described herein are associated with significant mortality and morbidity. Future research is much needed in three specific development areas: of biomarkers to aid the early detection of TLS and ARDS, of novel pharmacological therapies in the management of DIC and PRES, and of transplant strategies to reduce the risk of hematopoietic cell transplant-associated complications.

In the meantime, healthcare professionals involved in the care of oncology patients must be vigilant of oncology emergencies. Early recognition and prompt treatment can reduce the chances of potential complications and improve clinical outcomes, thereby improving not only survival rates in oncology patients but also their quality of life.

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