Review Article

Supportive care and symptom management in patients with advanced hematological malignancies: a literature review

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Background and Objective: Recent advances have led to cure or long-term disease control for patients with hematological malignancy (HM). Unfortunately, some of them still have poor prognoses and are often associated with significant symptom burden and poor quality of life for patients and families. These patients usually require supportive care including red blood cell and platelet transfusion, due to disease itself and the oncological treatment, apart from their symptom management. However, there is currently lack of the literatures review in these aspects. The objective of this review is to summarize practical supportive care recommendations for physicians or nurses practicing in palliative care (PC)/hematology-oncology unit, starting with core approaches in use of blood products for anemia and thrombocytopenia, management of tumor lysis syndrome, PC and oncology nursing care.

Methods: Evidence for this review was obtained from a search of the Cochrane database, PubMed, guidelines of European Society of Medical Oncology, British society of Hematology, American Society of Clinical Oncology, National Comprehensive Cancer Network and peer-reviewed journal articles.

Key Content and Findings: For asymptomatic cancer patients who are anaemic, a threshold of haemoglobin level of 7 g/dL is considered to be safe and generally favored for blood transfusion. 'Single-unit' red cell transfusion is safer and at least as effective as 'double-unit' transfusion. Prophylactic platelet transfusion should be given to stable patients without bleeding and with platelet count less than 10×109/L. In febrile patients, the threshold is lifted to 20×10^9/L. There are also recommendations for the use of blood products during COVID-19 pandemic. In general, HM patients were more prone to painful infections when compared with solid cancer patients. Thus, antibiotics to treat underlying infections should be applied whenever possible and as required to control pain.

Conclusions: This narrative review showed the recent literatures in the supportive care and symptom management of advanced HM patients. However, it is limited by some of the 'evidence-based' recommendations for interventions (including symptom management) based on early phase of HM populations rather than those receiving end-of-life care.

Keywords: Supportive care; symptom management; advanced haematological malignancies

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Introduction

The National Institute of Cancer defines supportive care as the care given to improve the quality of life of patients who have an advanced medical disease, with the purpose to reduce the symptom burden, resolve the psychosocial problems related to the disease or its treatment as early as possible (1). It usually refers to care to allow patients to complete treatments with minimal risk in hematological malignancy (HM) (2).

Despite advances in cure or disease control, some of these HM patients still have poor prognoses and are often associated with significant symptom burden and poor quality of life for patients and families. With incorporating an early palliative care (PC) model (3-5), there are increasing number of patients with advanced HM referred to PC team while they are still on disease-modifying treatment/therapy. While some of the principal management for symptoms are similar between solid and blood cancers, it is important to note that the approach in HM patients will be different because of the existence of multiple lines of treatments, difficulty in prediction of disease trajectory and requirements for blood transfusion. In fact, these patients usually require supportive care including red blood cell and platelet transfusion, due to disease itself and the oncological treatment, apart from their symptom management during their end-of-life (EOL) care (5). The supportive needs of family caregivers of these patients include psycho-social and practical issues (6). However, there is currently lack of the literatures review in these aspects. This article summarizes practical supportive care recommendations for physicians or nurses practicing in PC/hematology-oncology unit, starting with core approaches in use of blood products for anemia and thrombocytopenia, management of tumor lysis syndrome, PC and oncology nursing care. We present the following article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-691/rc).

Methods

Evidence for this review was obtained from a search of the Cochrane database, PubMed, guidelines of European Society of Medical Oncology, British society of Hematology, American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN), as shown in *Table 1* with detailed search strategy of one database (Table S1). HM diagnosis is based on the World Health Organization (WHO) diagnostic criteria (7).

This review includes articles through database searches on articles published from January 2001 to March 2022 with a focus on English language articles. In addition, we

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	5 April 2022
Databases and other sources searched	Cochrane database, PubMed, guidelines of European Society of Medical Oncology
Search terms used (including MeSH and free text search terms and filters)	Supportive care, haematological malignancies, symptom management, cancer, leukemia, lymphoma, myeloma, transplant
Timeframe	From 1st January 2001 to 31st March 2022
Inclusion and exclusion criteria	Inclusion: abstract, English, age ≥19 years; Exclusion: non-English articles, age <19 years
Selection process	2 authors (Chan KY & Chan TSY) conducted the selection independently. We reviewed bibliographies of selected articles for potentially relevant articles, and other articles recommended by experts in the field were included in this review. A third author (Gill H) reviewed any discrepancies for final consensus

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reviewed bibliographies of selected articles for potentially relevant articles, and other articles recommended by experts in the field were included in this review (*Table 1*).

In this narrative review, we discuss: (I) the types of supportive care related to medical aspects including transfusion of blood products, use of recombinant haematopoetic growth factors and treatment of infection in patients with HM; (II) symptom management related to diseases itself and also disease treatment adverse reaction.

Discussion

Transfusion of blood product

Transfusion of blood product is an integral part of care for patients with advanced HM. Cytopenia occurs as a result of the disease itself [e.g., myelodysplastic syndrome (MDS)] or chemotherapy. While the use of blood product could provide effective symptomatic relief, judicious prescription is also important to avoid unnecessary risks associated with transfusion and to economize their usage. Transfusion is best viewed as a short-term management strategy with mixed risk-benefit profile, and emphasis should also be placed at the underlying diagnosis, which should be treated according (8). Three types of blood product are commonly prescribed in PC setting.

Red cell transfusion

Anaemic patients have reduced haemoglobin (Hb) concentration and therefore impaired tissue oxygen delivery. Red blood cell transfusion helps improve symptoms and the deleterious effects on different organ systems. Recent literatures showed favorable associations between the transfusion and patient-reported symptoms (9,10). For haemodynamically stable, asymptomatic patients, a restrictive strategy with a Hb trigger at 7 g/dL is recommended. Most trials in this review compared restrictive (trigger at 7 g/dL) versus liberal (trigger at 10 g/dL) strategies. There were no differences in the functional recovery, length of in-patient or intensive care unit stay, risk of myocardial infarction and 30-day mortality. However, the probability of patients receiving a transfusion decreased by 41% in restrictive group (11). Two subsequent large retrospective cohort studies (12,13) showed similar results. A transfusion trigger of 7 g/dL is also consistent across several international guidelines (14,15).

However, the recommendation may not be applicable to all patient categories, primarily due to the lack of strong evidence in specific subgroups. For example, this recommendation is invalid in patients with chronic anaemia requiring recurrent transfusions (16). There is also no recommended value of trigger in patients with advanced HM. Despite the lack of strong evidence, for asymptomatic cancer patients who are anaemic, a threshold of 7 g/dL is considered to be safe and generally favored (*Table 2*) (15,17).

The routine practice of 'double-unit' blood transfusion should be discouraged. 'Single-unit' transfusion is safer and at least as effective as 'double-unit' transfusion (18,19). In haemodynamically stable patients, single-unit blood transfusion should be considered, with the patients reassessed by clinicians for any on-going symptoms for further transfusion (14,15).

Platelet transfusion

The threshold for platelet transfusion has been well defined and is consistent with international guidelines (20-22). Prophylactic transfusion should be given to stable patients without bleeding and with platelet count less than 10×10^9/L. In febrile patients, the threshold is lifted to 20×10^9/L (*Table 2*). There are rare situations in which platelet transfusion may be contraindicated/not recommended. For example, in immune thrombocytopenia without bleeding, when prophylactic platelet transfusion is considered futile. In thrombotic thrombocytopenic purpura (TTP)/heparin induced thrombocytopenia (HIT), prophylactic platelet transfusion is considered to aggravate the thrombotic process. Haematologists should be consulted when such problems arise (17). The usual adult dose is four random donor units or one apheresis platelet unit. Each unit of random donor platelets should be able to raise the platelet count by $7–10\times10^9$/L (17).

Refractoriness to platelet transfusion may occur, and in PC setting this is most often due to formation of antibodies against human leucocyte antigen (anti-HLA antibodies), as a result of multiple transfusion and HLA-alloimmunization. Typically, these patients demonstrate insignificant rise in platelet counts in the early (ten minutes to one hour) post-transfusion samples. Transfusion of HLA-matched platelets could circumvent such problem, and a prior arrangement with the blood bank is needed. Clinicians should also consider substitutes to reduce the risk of bleeding, especially in the presence of blood product shortage. The use of fibrinolysis inhibitor, tranexamic acid is an effective adjunct in reducing bleeding risk (17). If there is a shortage of blood

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Table 2 Trigger and use of blood products in patients with advanced haematological malignancies

Blood products	Trigger	Remarks
Packed cells transfusion	Hb <7 g/dL for hemodynamically stable	Single unit recommended; Invalid in patients with chronic anaemia requiring recurrent transfusions
Platelet	$<10\times10^9$/L if stable	Prophylactic platelet transfusion is considered futile in immune thrombocytopenia without bleeding
	$<20\times10^9$/L if febrile	Contraindicated In TTP/HIT
	Low threshold for platelet transfusion if there are bleeding symptoms or when clinical interventions are planned	
Plasma transfusion	For patients with multiple coagulation factors deficiencies, especially during the settings when clinical procedure is planned	
G-CSF	For febrile patients if ANC <1.0	Absolutely contraindicated in patients with acute promyelocytic leukemia
	Recommended for prophylactic use if the risk of chemotherapy-induced febrile neutropenia is higher than 20%	Regular G-CSF use may reduce incidence of documented infection, febrile neutropenia and duration of hospital stay. The main side effect is bone pain secondary to stimulated bone marrow activity
ESA	Recommended for regular use in patients with low to intermediate risk MDS	Need to monitor blood pressure Caution for use in patients with malignancies
TPO-RA	Labelled indication includes immune thrombocytopenia, hepatitis C patients receiving interferon treatment with thrombocytopenia and severe aplastic anaemia	

Potential risks, benefits and patient's goals should be considered as a whole. Hb, haemoglobin; TTP, thrombotic thrombocytopenic purpura; HIT, heparin induced thrombocytopenia; G-CSF, granulocyte colony stimulating factors; ANC, absolute neutrophil count; ESA, erythropoiesis stimulating agent; MDS, myelodysplastic syndrome; TPO-RA, thrombopoietin receptor agonist.

supply or suitable human leukocyte antigen-matched units during COVID-19 pandemic, prophylactic antifibrinolytics should be considered for patients with low platelet counts ($<10\times10^9$/L) (23).

Plasma transfusion

In PC setting, use of plasma and plasma-derived products is relatively uncommon. Fresh frozen plasma (FFP) is mainly used to replace multiple coagulation factors deficiency, examples include disseminated intravascular coagulation (DIC), end-stage liver failure or warfarin overdose. For fibrinogen replacement, cryoprecipitate should be used [e.g., in acute promyelocytic leukaemia (APL)]. A consultation with haematologists, if these products are to be used, is strongly encouraged (17).

Special blood product preparations

Irradiation inactivates the lymphocytes contained in the blood product, thereby mitigating the risk of transfusion associated graft-versus-host disease (TA-GVHD). Irradiation is therefore needed in those situations in which the recipient is profoundly immunocompromised. However, the definition of such immunocompromised state is controversial (17). International guideline stipulates the need of irradiation in the following conditions: (I) Recipient of allogeneic or autologous haematopoietic stem cell transplant; (II) Prior treatment with purine analogues (cladribine, clofarabine, fludarabine, bendamustine), anti-thymocyte globulin (ATG) or anti-CD52 antibody (alemtuzumab); (III) Patients with Hodgkin lymphoma. Clinicians should alert the blood bank if the patients have any of the conditions above (17). Blood bank would then provide irradiated blood products for these patients indefinitely, unless specifically requested otherwise by clinicians.

Leucodepletion is a measure to reduce the amount of leucocytes contained in the blood products. Reduction in leucocytes would hence reduce the risk of febrile non-haemolytic transfusion reaction and HLA-alloimmunization. For those patients with chronic transfusion needs, leucodepletion is recommended (17).

Cytomegalovirus (CMV)-negative blood products are

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reserved to those who are serologically negative for CMV (i.e., they have not contracted CMV before and therefore immunologically naïve). This is meant to prevent primary CMV infection through blood borne transmission (17).

Recombinant haematopoietic growth factors

Recombinant haematopoietic growth factors play an important supportive role in the management of HM. The three types of growth factors which are commonly used in the PC setting will be discussed (17).

Erythropoiesis stimulating agent (ESA)

ESA is recommended for the treatment of low to intermediate risk MDS (*Table 2*). In these patients, the use of ESA reduces frequency of red cell transfusion and improves quality of life. There is no optimal dose or schedule of administration. In general, the dose used in the treatment of anaemia in MDS would be higher than that of anaemia in chronic renal failure. Thromboembolism and hypertension are two important complications associated with ESA therapy. Clinicians should remain vigilant when managing patients on ESA (17).

Granulocyte colony stimulating factors (G-CSF)

Major international guidelines recommend the use of prophylactic G-CSF if the risk of chemotherapy-induced febrile neutropenia is higher than 20% (24-26). Its use primarily results in reduced incidence of documented infection, febrile neutropenia and duration of hospital stay, while the effect on survival is less clear (27). G-CSF has been extensively used in hematology cancer patients. The main side effect is bone pain secondary to stimulated bone marrow (BM) activity (*Table 2*). Outpatient administration of G-CSF is recommended for lower-risk patients during COVID-19 pandemic (23). The only absolute contraindication for G-CSF injection is untreated APL in which the leukaemic cells are exquisitely sensitive to G-CSF driven proliferation. The use of G-CSF in this setting might cause a rapid expansion of leukaemic clone, which may be life-threatening (27).

Thrombopoietin receptor agonists (TPO-RAs)

Romiplostim and eltrombopag are peptide and non-peptide TPO-RAs, respectively. They act on thrombopoietin receptor in megakaryocytes and therefore stimulate platelet production (17). They have been used extensively in various conditions associated with thrombocytopenia (*Table 2*). Labelled indication includes immune thrombocytopenia (eltrombopag and romiplostim), hepatitis C patients receiving interferon treatment with thrombocytopenia (eltrombopag) and severe aplastic anaemia (eltrombopag). Eltrombopag has also been used in patients with MDS or chemotherapy induced thrombocytopenia. Eltrombopag is more commonly prescribed because of its oral tablet formulation (while romiplostim has to be injected because of its peptide structure). The major side effect of eltrombopag is liver enzyme derangement, which is reversible (17).

Other agents of interest

Luspatercept is a novel erythroid maturation agent which can improve anaemia by stimulating late erythroid maturation, by binding to select transforming growth factor β ligand super family and reducing SMAD2 and SMAD3 signaling. It has been tested in clinical trial (MEDALIST trial) (28) to improve anaemia in low risk MDS patients with ring sideroblasts. The side effects are mild and include diarrhea and fatigue.

Infection in patients with HM

Patients with advanced HM are often immunocompromised as a result of their primary conditions or the treatment given. The development of opportunistic infections carries significant morbidities and mortalities (29). It is important for the PC physicians to be vigilant against the occurrence of these infections and deliver treatment promptly. In this section, prophylaxis and treatment of common opportunistic infections will be discussed.

Bacterial infections

Anti-bacterial prophylaxis

The use of anti-bacterial prophylaxis could potentially reduce the incidence and mortality associated with bacterial infection in a neutropenic host. However, the benefits of such strategy have to be weighed against the risks (e.g., gastrointestinal toxicity of antibiotics, clostridium difficile infection, promotion of antibiotic resistance, etc.). In general, anti-bacterial prophylaxis is reserved for patients at high risk of developing neutropenic fever.

Guidelines jointly published by ASCO and the Infectious Diseases Society of America (IDSA) (29) recommend prophylaxis in patients at high risk of febrile neutropenia. Examples of high-risk patients including patients with leukaemia receiving induction chemotherapy, patients who are

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recipients of allogeneic haematopoietic stem cell transplant (HSCT) in pre-engraftment period, or any patients who are expected to have more than seven days of neutropenia with neutrophil count less than 0.1×10^9/L. A meta-analysis (30) of 109 studies involving 13,579 patients showed that in high risk patients, fluoroquinolone prophylaxis resulted in reduction of febrile episodes/patients and all-cause mortality with a relative risk of 0.79 and 0.57, respectively). Although in low-risk patients (primarily those with solid tumours), reduction in febrile episodes/patients and all-cause mortality were also seen, the number needed to treat (NNT) to prevent one death in low-risk group (NNT=63) was much higher than that in the high-risk group (NNT=29). The guideline committee therefore decided that the benefits outweigh the harms in the latter. Fluoroquinolones are the agents of choice. Both ciprofloxacin and levofloxacin are acceptable. While ciprofloxacin possesses stronger *in vitro* activity against pseudomonas species, levofloxacin has a better pharmacokinetic profile (thus enabling daily dosing) and a better coverage for gram positive organisms. It is important also to watch out for prolongation of corrected QT interval while patients are put on these agents (30).

Empirical treatment of febrile neutropenic patients

In patients with neutropenic fever, around 10–30% suffer from bacteraemia (30-32). However, all patients would require empirical antibiotics therapy as there is yet a reliable tool to differentiate patients who have genuine bacteraemia versus those who do not. It is important to cover for gram-negative rods (e.g., Escherichia Coli, Pseudomonas species, etc.) as they are particularly virulent and have strong association of sepsis. In older studies, unopposed gram-negative bacteraemia without appropriate empirical antibiotics carry a mortality of 70% in neutropenic patients (33,34). The timing of empirical antibiotics is also important, as each hour of delay could lead to 18% increase in 30-day mortality (35). It is recommended that the first dose of antibiotics should be given within one hour of onset of fever. When considering the choice of first line empirical antibacterial, the local epidemiology and resistance patterns have to be taken into account. In general, agents that are active against pseudomonas (e.g., piperacillin-tazobactam) have to be used. In patients who have a history of infection or carriage of extended beta-lactamase producing organism, carbapenem group of antibiotics should be given.

Expert advice from microbiologists must be sought, in case if the patient is a known carrier of carbapenemase producing Enterobacteriaceae. In these situations, depending on the type of carbapenemase, stronger and more toxic antibiotics (e.g., colistin, avibactam-ceftazidime combination) might be used. The empirical antibiotics could be stopped after 72 hours if the patient remained afebrile for 48 hours irrespective of the neutrophil count, provided that if there is no septic focus identified. Patients with bacteraemia should receive 14 days of intravenous antibiotics therapy (34).

Special situations

In patients with persistent fever despite broad spectrum gram negative antibacterial coverage, infection caused by gram-positive organism is possible. Addition of gram-positive coverage (e.g., glycopeptides) is necessary in this setting. For persistent bacteraemia despite appropriate antibiotics, a further evaluation of the infective focus should be made. In patients with HM, colonization at the central venous catheter might be the related cause. Thus, it is suggested that both haematologists for consideration of catheter removal and microbiologists for antimicrobial use could be consulted if fever persists despite gram-positive and gram-negative coverage. Use of antifungal coverage will be indicated as next additive agent for second breakthrough fever. Escalation of antifungal may be necessary, as a prolonged neutropenia and prolonged use of broad-spectrum antibacterial might increase the risk of invasive fungal disease (34,35).

Fungal infections

Anti-fungal prophylaxis

Primary prophylaxis against both yeasts and moulds, which can cause serious invasive fungal diseases (IFDs) is recommended in patients with advanced HM. Candida species accounted for the vast majority of yeast infection while aspergillus species are responsible for most of the mould infection. Patients with prolonged (more than seven days) and profound neutropenia (neutrophil less than 0.1×10^9/L) are particularly susceptible to both types of fungus. Thus, agents that are active against both yeasts and moulds (e.g., echinocandins, itraconazole, posaconazole, voriconazole) are preferred in the contemporary guidelines (29,36) than mould-inactive agents (e.g., fluconazole) as primary antifungal prophylaxis. The strength of recommendations for each type of mould-active antifungals would differ and depends on the availability of well-conducted trials. For instance, capsule formulation of oral itraconazole at 200 mg twice daily is the standard primary antifungal prophylaxis and intravenous

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micafungin at 50-100 mg daily is reserved for patients who are unable to tolerate oral drugs. Primary prophylaxis for fungal infection by itraconazole oral solution (ITCZ-OS) harbors better bioavailability than capsule (36).

Secondary prophylaxis is recommended in patients who have a history of prior IFDs, continuation of the antifungal after initial control is necessary to prevent recurrence when they receive subsequent chemotherapy. This is best studied in aspergillus infection, and voriconazole is usually the agent of choice. *Pneumocystis jirovecii*, which is now considered to be a fungus, causes opportunistic infection in patients with impaired cell-mediated immunity. This is particularly important in patients who received allogenenic HSCT, glucocorticoid therapy or lymphocyte depleting chemotherapy (e.g., fludarabine). In these patients, co-trimoxazole is a standard prophylactic agent. In anti-fungal treatment including prophylactic use, the positioning and role of liposomal amphotericin (or amphotericin) would be reasonably added. If the patient is allergic to co-trimoxazole or glucose-6-phosphate dehydrogenase (G6PD)-deficient, inhalation of pentamidine is an effective alternative (29,36).

Anti-fungal treatment

Treatment of established fungal infection is usually given in the acute care setting. The choice of agents depends on various factors, including the underlying haematological condition, the site of infection, prior antifungal use and (preferably) results of *in vitro* antifungal susceptibility testing. In general, echinocandins are the first-line agent for the treatment of invasive candidiasis, while voriconazole/isavuconazole are the agent of choice in invasive aspergillosis (37). Microbiologists can be consulted in these situations.

Viral infections

Herpesviridae is a family of viruses which is characteristic of its capability of reactivation after long latency period in human host. These viruses also commonly cause problems in patients with HM. Herpes simplex virus is capable of causing herpes labialis, herpes gingivostomatitis, genital and perianal herpes. They are easily treated with oral valacyclovir 1,000 mg twice/day for one week or acyclovir 400–800 mg five times/day (with dosage adjustment in renal impairment) (38).

Varizella-zoster virus can cause either dermatomal zoster (herpes zoster) or disseminated zoster infection. A high index of suspicion is need as sometimes patients might present with pain before appearance of blisters. They are treated with higher dose of valacyclovir at 1,000 mg three times per day for ten days (38).

CMV could result in several serious clinical syndromes, including CMV retinitis, colitis and pneumonitis. A long latency is present between detectable CMV viral replication in blood and clinical disease. Pre-emptive treatment therefore forms an important strategy in the prevention of CMV diseases. Treatment options include intravenous ganciclovir (at 5 mg/kg every 12 hours), oral valganciclovir (at 900 mg twice daily) or intravenous foscarnet (at 90 mg/kg every 12 hours). One of the major side effects of ganciclovir/valganciclovir is myelosuppression. For foscarnet treatment, electrolyte imbalance and nephrotoxicity are the major complications (38).

Specific hematology-oncology emergencies

In acute myeloid leukaemia (AML), leucostasis appears at leucocyte counts above 100×10^9/L, and severe symptoms appear above 400×10^9/L in acute lymphoblastic leukaemia (ALL). Management of symptomatic leucocytosis include adequate hydration and premedication with xanthine oxidase inhibitors (febuxostat/allopurinol) with or without rasburicase (ensure G6PD normal); hydroxyurea (50–100 mg/kg/day) which results a rapid cytoreduction in AML; specific chemotherapy; and leucocytapheresis is rarely necessary but will be considered in cases of hyperleucocytosis secondary to AML with signs of leucostasis (39,40) (*Table 3*). However, its use in ALL is controversial (41). The most frequent conditions associated with blood hyperviscosity syndrome (HVS) include hyperleucocytosis and Waldenstrom's macroglobulinemia. The management of hypercalcemia (42) and cord compression (43) will be discussed in *Table 3*. The role of surgery in cord compression is minimal as HM patients usually respond rapidly to radiotherapy and chemotherapy as well as steroids.

Principles of symptom management

Symptoms can be due to cancer itself or related treatments. Common symptoms related to disease treatments include peripheral neuropathy (e.g., bortezomib, thalidomide), fatigue (e.g., carfilzomib, lenalidomide), vomiting (e.g., cyclophosphamide, melphalan, elotuzumab, vorinostat), rash (thalidomide, Pomalidomide) and edema (carfilzomib,

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Table 3 Management of haematologic emergencies

Hematological emergencies	Management
Hyperleucocytosis	Treatment of symptomatic leucocytosis includes:
	• Adequate hydration
	• Premedication with xanthine oxidase inhibitors (febuxostat/allopurinol)
	• With or without rasburicase (ensure G6PD normal); hydroxyurea (50–100 mg/kg/day) which results a rapid cytoreduction in acute myeloid leukemia; specific chemotherapy; and leucocytapheresis is rarely necessary
Hypercalcemia	Multiple myeloma is the commonest cause and hypercalcemia is caused by PTH-related peptide secretion in about 80% of the cases
	Treatment includes:
	• Rehydrate accordingly
	• Consider pamidronate 30–90 mg in 250 mL^{-1} L normal saline to infuse over 2–24 hours
	• For hypercalcemia resistant to pamidronate, consider zoledronate 4 mg IV infusion over 15 minutes
	• Recheck blood parameters after 1 week
	• Bisphosphonate is generally contraindicated if creatinine clearance <30 mL/min
	• Denosumab (e.g., 120 mg SC every 4 week) is an option for patients with hypercalcemia that is refractory to zoledronic acid or in whom bisphosphonates are contraindicated due to severe renal impairment
	• Consider steroid e.g., Prednisolone 30 mg or hydrocortisone 100 mg IV q6h for hypercalcaemia in myeloma and lymphoma
Cord compression	Use of magnetic resonance imaging would be the method of choice for detecting spinal compression
	Treatment includes:
	• Steroids: not enough data for the optimum dosage and duration. Some clinicians administer a starting dose of 10 mg of dexamethasone, followed by 4 mg every six hours for 2–3 days and then reducing doses
	• Radiotherapy: to spine
	• Decompressive surgery: minimal role as the patients with haematologic malignancies usually respond rapidly to radiotherapy and chemotherapy as well as steroids

Potential risks, benefits and patient's goals should be considered as a whole. G6PD, glucose-6-phosphate dehydrogenase; PTH, parathyroid hormone; IV, intravenous; SC, subcutaneous.

lenalidomide, dexmethasone) (44). Routine assessment of symptom severity by numerical rating scale (NRS) is recommended as it is convenient and reliable, although other factors such as education background, timing and activities have to be assessed (5).

Anorexia

Very often, advanced HM patients will experience loss of appetite and may lose weight especially at the time of high dose chemotherapy and stem cell transplant, when significant weight loss may occur in a short period of time. Management of those contributors to anorexia, such as nausea, constipation, or dyspnea, might help. Dietician can be consulted to provide practical and safe advice for feeding although it is not mandatory for these patients (45).

Corticosteroids can improve appetite over a few days, but chronic use should be avoided because of their long-term adverse effects (46,47). For more prolonged appetite stimulation, the progestogen megestrol acetate can be used at doses of 80–160 mg daily, titrating upwards to no more than 800 mg per day (*Table 4*). Corticosteroids and progestin have been initially proposed to treat cachexia, showing significant improvement in body weight and appetite. Combination treatment (carnitine (4 g/day) plus celecoxib (300 mg/day) with or without megestrol) has been used with satisfactory improvement (appetite, body weight and physical activities)

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Table 4 Summary of treatment options for common symptoms (non-pain) in patients with advanced hematological malignancies

Symptom	Treatment
Anorexia	• Optimizing management of major contributors to anorexia, such as chronic nausea, constipation, taste alterations, dyspnea, and depression
	• Short course of steroid (i.e., dexamethasone 4 mg daily for maximum of 7 days)
	• Megestrol acetate 80–160 mg daily, titrating upwards to no more than 800 mg per day
	• Referral to dietitian (optional)
Fatigue	• Treating symptomatic anaemia with blood products transfusion, ESA and iron supplements
	• Correct underlying electrolyte disturbance, such as hypercalcemia and hyponatremia
	• Consider both pharmacological and non-pharmacological measures e.g., exercises
	• Look for depression
Nausea and vomiting	• Screen for potentially reversible causes like severe constipation
	• Gastroparesis by prokinetic agents such as metoclopramide 5–10 mg TDS, domperidone 10 mg TDS (be aware of extrapyramidal side effects)
	• Uraemia and opioid-induced causes by central anti-dopaminergic drugs such as haloperidol 0.5–5 mg BD
	• Brain tumour cause by dexamethasone and consider for radiotherapy
	• Anti-emetics such as 5-hydroxytryptamine 3 antagonist, natural killer-1 antagonist, olanzapine and dexamethasone for chemotherapy-induced
	• Cannabinoids may be helpful in treatment of nausea and vomiting but are not well studied
Pruritus	• Antihistamines include hydroxyzine at doses of 10 to 25 mg at night are usually considered first
	• Selective serotonin reuptake inhibitors [e.g., paroxetine (5 to 20 mg/day), sertraline (25 to 50 mg), mirtazapine (15 to 30 mg/day) and fluvoxamine (25 to 100 mg/day)] or gabapentinoid [e.g., gabapentin (300 mg, up to 3,600 mg maximum daily divided in up to three doses) and pregabalin (75 mg, up to 600 mg/day divided in up to three doses)] may also be effective as antipruritic therapies
	• Course of steroid has been reported to be effective in management of pruritis in lymphoma patients not responding to above therapies
	• Other agents to consider in patients with refractory pruritus include thalidomide, naltrexone, butorphanol, and aprepitant
Depression	• Screening by single-item assessment: are you feeling depressed?
	• Assess and control physical symptoms, especially pain and fatigue
	• If appropriate, withdraw drugs that contribute to depressed mood
	• Provide psychological support: provide options to patient, facilitate adaptive coping, maintain realistic hope
	• Consult clinical psychologist
	• Start anti-depressant, e.g., fluoxetine 20 mg daily or other SSRI, SSNRIs, TCAs

Potential risks, benefits and patient's goals should be considered as a whole. ESA, erythropoietin stimulating agent; TDS, three times a day; BD, twice daily; SSRI, selective serotonin reuptake inhibitor; SSNRI, selective serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

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in solid cancer patients but this has not been tested in patients with advanced HM (47). The evidence is inconclusive regarding the benefits of other treatments for anorexia-cachexia syndrome, including olanzapine, anamorelin, cyproheptadine, long-chain omega-3 fatty acids, vitamins, minerals, and other dietary supplements, and thalidomide (48-50).

Fatigue

Patients with acute leukemia (61%) reported higher degree of fatigue when compared with other types of HM (51). Non-pharmacological interventions for cancer-related fatigue (CRF) include correction of any reversible factors such as anaemia, infection and electrolyte disturbances, impacting on fatigue. For instance, adjusting the anticancer treatment or dose could be useful if the CRF was thought to be related to the tumour itself or its treatment. Erythropoiesis-stimulating agent (ESA) has important roles in MDS patients apart its indications in post-chemotherapy anaemia treatments for both HM and solid cancer patients (52,53). ESAs can be considered for MDS patients with symptomatic anaemia to correct and maintain Hb levels (52,53) or help to reduce symptoms transiently in case of severe anaemia (53). Intravenous/oral iron could also be indicated for patients with low iron levels as mentioned in *Table 4* (54). All the above measures have been proven to reduce fatigue severity or improve quality or life in cancer patients with low Hb levels and/or anaemia (55). Bisphosphonates can be prescribed for the treatment of hypercalcaemia (42) while fluid restriction could be considered in hyponatremia (56).

Sleep disturbance often occurs in advanced HM patients with different degree of fatigue levels (57). Benzodiazepine (e.g., short-acting) treatment could be indicated in patients with persistent insomnia or those do not respond to medications (55). In case of disturbed circadian rhythm, sedating antihistamines, antidepressants or methylphenidate can also be considered (58). There is a growing body of literature to support the role of exercise in the management of CRF (59,60). Other non-pharmacological measures include energy conservation which is shown to be a useful strategy for advanced HM patients, assisting them to lessen them the degree of energy depletion. In addition, use of daily self-monitoring of fatigue levels might provide a balance of routine and activities according to fatigue pattern (55).

Pain

In HM patients, bone is the principal source of somatic pain (61,62). This includes sensory and sympathetic nerve fibers richly and extensively supply the periostium, the mineralized bone and the BM (63). Most pain syndromes experienced by multiple myeloma (MM) (62). Beyond MM, the same kind of skeletal lesions may also occur in the course of several advanced HM disease, although less commonly observed (64). Allogeneic HSCT patients might experience pain associated with GVHD-related mucosal damage, which has a similar appearance to that caused by cytotoxic drugs (65).

Both pharmacology and non-pharmacology measures including procedural interventions, behavioral methods, and supportive care are necessary to achieve effective pain management (66). Pharmacological modalities for pain management in HM patients are based on analgesic (opioid and nonopioid) and adjuvant agents. The choice of the analgesics will depend on the types of pain (nociceptive/neuropathic/other causes), availability of analgesics, concurrent medications (the risk of drug interactions) and the co-morbidities (i.e., liver/renal failure/chronic illnesses) (67,68). This should be taken into considerations for the effects on the tolerability and efficacy of use of analgesics. Based on WHO analgesic ladder, nociceptive pain could be controlled by standard analgesics, such as paracetamol, weak/strong opioid and nonsteroidal anti-inflammatory drugs (NSAIDs) while co-analgesics e.g., gabapentin are preferred for neuropathic pain (*Table 5*). In general, HM patients were more prone to painful infections (e.g., wound infections, oral mucositis) when compared with solid cancer patients. Thus, antibiotics to treat underlying infections should be applied whenever possible and as required to control pain (62).

Opioids remain one of the most prescribed pain medications in PC (68). In fact, tramadol, which is a combination of weak opioid and serotonin-norepinephrine reuptake inhibitor (SNRI), has a number of side effects (e.g., dizziness, fatigue) and drug interactions (as an SNRI, cytochrome inhibitor etc.), thus has fallen out of favor for treatment. In general, many clinicians would avoid the second step of the WHO ladder and start with a strong opioid albeit at a lower dose for cancer patients. Short-acting opioids are used for intermittent pain on needed basis (*Table 5*). Incidental pain and other breakthrough pain might require rescue doses of a rapidly short-acting agent, as on-demand doses or for procedures or related to movements that might aggravate the pain (68). For the treatment of GVHD-related mucositis, opioids (e.g.,

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Table 5 Management of pain symptoms in patients with advanced hematological malignancies

Identify the type of pain syndromes: (somatic/visceral/neuropathic) and establish etiology of pain

Holistic assessment of severity of pain and its effects on physical/psychological/social/spiritual aspects

Assessment of severity of pain: Numerical rating scale/Verbal rating scale

Monitor progress of pain control

Analgesic ladder

- Patients with mild pain should be started on non-opioids (e.g., paracetamol), moderate to severe pain on weak opioids (e.g., Tramadol 50 mg qid) or low dose strong opioids (e.g., morphine 2 mg q4h) and over-whelming pain on strong opioids (e.g., morphine 5–10 mg po q4h), together with adjuvants as necessary
- Analgesics are given on a regular basis, with pro re nata prescription for breakthrough pain, e.g., in the case of morphine, 10–20% of the total daily dose of morphine q1h as required. Short-acting opioids are used for intermittent pain on needed basis
- Laxatives should be prescribed on starting morphine (e.g., senokot 2 tab bd), unless contra-indicated
- Fentanyl/methadone is the drug of choice for patients with advanced renal failure

Special considerations:

Graft versus host disease or related mucositis

- Opioid (e.g., morphine) could be administered by continuous intravenous infusion or a patient-controlled analgesia delivery system if oral route is not possible

Neuropathic pain

- Consider adjuvants of gabapentin 1,800–2,600 mg/day/pregabalin 300–600 mg/day/venlafaxine 150–225 mg/day/duloxetine 30–60 mg/day
- Beware of use of tramadol together with duloxetine for theoretical potential complication of serotonin syndrome

Liver capsular pain

- Dexamethasone (4–8 mg om + noon) may be used as co-analgesic for distending capsular pain in hepatomegaly or liver metastasis to reduce hepatic edema and liver pain. However, there is lack of high-quality clinical trials on its use
- Beware of co-existence of hepatitis B or C especially in patients with hematology cancer, for which use of steroid may lead to flare up of the virus

Bisphosphonates for bony metastasis

- Compared with placebo or no bisphosphonates, treatment with bisphosphonates significantly improved bone pain in most clinical studies
- e.g., zoledronate 4 mg/pamidronate 60 mg

Denosumab (e.g., 60/120 mg sc) might have analgesic effect

Non-steroidal anti-inflammatory drugs

- Beware of gastric side effects and add proton pump inhibitors for gastric protection, caution for any renal toxicity

Other oncological treatments

- Consider referral for radiotherapy for painful bony metastasis

Interventional anesthetic procedures

- Intrathecal pump implantation can be considered for uncontrolled pain with severe side effects from analgesics despite conventional treatments of side effects or opioid switching

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morphine) can be given orally to the patients in the first place. However, this could be administered by continuous intravenous infusion or by a patient-controlled analgesia (PCA) delivery system if oral route is not possible. There is no significant difference in analgesia between PCA and continuous opioid infusion, except that PCA is associated with reduced opioid requirements and pain duration (69). Prolonged infusion of morphine may be needed. If there are dose-limiting adverse effects occurred, rotation to another opioid (e.g., fentanyl) can produce improvement in the majority of patients, without loss of pain control (70). Transdermal opioids such as fentanyl patches offer an alternative route in patients with mucositis or GVHD. It was shown that transdermal fentanyl patch was found to be effective in both relieving oral mucositis pain with excellent tolerability and improving the quality of life for hematological patients with mucositis receiving high-dose chemotherapy (71). However, these patches are specifically contraindicated in opioid naïve patients and should preferred to be started in patients with stable opioid consumption. Methadone might offer therapeutic effect on neuropathic pain as related to its N-methyl-D-aspartate antagonist properties. In patients with advanced renal failure, fentanyl or methadone is the drug of choice for strong opioid use. However, specific cautions are needed for the use of methadone in view of its long half-life and drug-drug interactions (68).

Coanalgesics, (also known as adjuvant analgesics) are medications when added to primary analgesics that reduce pain to a lesser degree of severity. Although opioids e.g., tramadol might used to treat neuropathic pain, coanalgesics are often used together with opioids for neuropathic pain treatment (63). First-line options for neuropathic pain include selective serotonin norepinephrine reuptake inhibitors (SSNRIs), tricyclic antidepressants (TCAs), or anticonvulsants such as gabapentin/pregabalin. The effective analgesic dosage of TCAs is often effective less than that target for depression treatment. This includes nortriptyline 10–150 mg/day or desipramine 10–200 mg/day orally—they must be started at low doses and then titrated every 4–6 days if necessary. SSNRI medications include venlafaxine 150–225 mg/day, duloxetine 60 mg/day or 20 mg twice-daily for older people. Gabapentin usually starts at 100–200 mg orally, twice-daily and titrated up to maximum dosage to 1,800–2,600 mg/day (*Table 5*). Pregabalin can be given initially at 150 mg/day in 2 to 3 divided doses and then titrated up to 300–600 mg/day (63). Starting doses for gabapentin and pregabalin should be considerably lower especially for older patients or those with renal failure. Bisphosphonates or denosumab might be effective (42).

Nausea and vomiting

Guidelines for anti-emetics have been well established by the ASCO and the NCCN (72,73), which recommend the use of a 5-HT3 antagonist, Neurokinin-1 (NK1) receptor antagonist, olanzapine and dexamethasone for highly emetogenic chemotherapy (*Table 4*). Radiation to the upper abdomen is considered moderate emetogenic risk, and guidelines recommend patients receive a 5-HT3 antagonist before each fraction of radiation. Adding dexamethasone for treatments might provide additional prophylaxis. Cannabinoids might be useful for the treatment of nausea and vomiting, however they are not well studied (74).

Pruritus

A number of drugs, such as H1 antihistamines, corticosteroids, antidepressants, gabapentinoids, opioid antagonists, and NK1 receptor antagonists have been used to control pruritus in this patient population, as reported in small uncontrolled studies or case reports. There are no comparative trials, and the choice of initial therapy is empiric. As in other conditions associated with pruritus, antihistamines (e.g., hydroxyzine at doses of 10 to 25 mg at night) can be considered first (75).

In refractory cases, SSRIs, SNRIs or gabapentinoid drugs are usually considered, and might be used on combination if needed. Moderate and usually rapid-onset (within days) antipruritic effects have been suggested in some studies with paroxetine (5 to 20 mg/day), sertraline (25 to 50 mg) and fluvoxamine (25 to 100 mg/day). Sertraline was shown to have satisfactory antipruritic effects in advanced renal failure patients (72). In several case reports, mirtazapine (15 to 30 mg/day) has also demonstrated antipruritic effects as well (*Table 4*) (75-78).

The gabapentinoids-gabapentin (300 mg, up to 3,600 mg maximum daily divided in up to three doses) and pregabalin (75 mg, up to 600 mg/day divided in up to three doses) may also be effective as antipruritic therapies (63). The mechanism of action is likely a combination of central inhibition of pruritus perception, decreased excitability of spinal and supraspinal neurons, and inhibition of serotonergic circuits. Gabapentin in combination with mirtazapine was found to be helpful in relieving pruritus in patients with Cutaneous T-cell lymphoma (CTCL) (75).

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Use of steroid, such as prednisone (30 to 40 mg) or thalidomide has been found to be effective for treatment of pruritus in lymphoma patients (75) while these have seldom been reported in other malignancies.

Psychosocial and existential distress

Major depression occurs in 25% or more of patients with advanced cancer (79). NCCN has recommended screening of all cancer including HM patients for depression. A single-item screening tool ("Are you feeling depressed?") has been shown to be useful for identifying depression (80). Both antidepressants and psychotherapy have shown efficacy in treating depression in patients with advanced malignancies (81,82). SSRIs, TCAs, SSNRIs are all antidepressants associated with time lag (about 4 week) before taking the clinical benefits. Other medications including mirtazapine, trazodone, and buproprion, can be used as second agents if there is inadequate response to first line agents. It is necessary to consult psychiatrist in case of uncertain diagnosis or complex medication choices (82).

About 20% of cancer patients experienced persistent anxiety symptoms (79,83). Anxieties commonly occurs in advanced HM patients while they are receiving disease treatment. They usually worry about their disease course, side effects of treatment and difficult in caring (especially those elderly). Mental disorders, poorly controlled physical symptoms, lack of social support are the associated factors for anxiety (79). Management of anxiety should consist of maximized control of symptoms especially pain, and dyspnea. Pharmacological treatments of acute anxiety include benzodiazepines and for chronic anxiety include SSRIs. Complementary therapies such as massage therapy or music therapy might have a role in anxiety therapy. Psychotherapy might also be useful (84-86).

End of life care

"Good death" is highly individualized with several important elements of having a sense of closure, feeling valued or recognized as an individual, accepting the appropriateness of death, minimizing burdens to others, and preparing the family (87,88). Although home death is an option, patients with HMs remained more likely to die in the hospital (89). One domiciliary program showed that supportive care (transfusion of blood products, antibiotic treatment) and symptom management at home could contribute to better outcomes for a group of HM patients (90). Some patients might prefer less intensive treatments during their EOL care. Use of oral targeted therapy has been shown to reduce time in cancer center in certain HM conditions (91).

Nursing care

The roles of PC nurse include symptom management, emotional and practical support (e.g., Hickman line) to patients and their families. Patient-centred and continuum of care from diagnosis to bereavement is very important. In this context, nurses are expected to have equipped with skillful communication and listening. The information about disease prognosis and adverse effects of treatment is offered with sensitivity if patients are ready (87). Acknowledge patient and family for the possibility of sudden deterioration and death due to catastrophic bleed or infection would prepare them for their acceptance. Care of central venous access devices is the essential part of nursing care in HM patients (*Table 6*) (92). On the other hand, the hematology nurse would be expected to have basic PC competencies and skills (93).

Conclusions

This narrative review showed the recent literatures in the supportive care and symptom management of advanced HM patients. Although it is comprehensive, there are several limitations. The guidelines provided for transfusion (e.g., triggers for blood products) are based on data applying to mortality rather than patient comfort. There is limited data on pain syndromes in advanced HM. Moreover, some of the 'evidence-based' recommendations for interventions (including symptom management) are drawn from early phase of HM populations or solid malignancies. Thus, all the management plans should require careful consideration of the potential risks and benefits and must consider a patient's goals and wishes. Further studies regarding the PC management for advanced HM are highly warranted.

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Table 6 Nursing care of central venous access devices

(A) Catheter handling

1. Scissors, scalpels, safety pin, sharp-edged or toothed clamps/forceps should never be used near the catheter
2. Clamp catheter on the clamping sleeve only
3. To prevent catheter pulling or accidental dislodgement:
   - No pulling force exerted onto the catheter
   - Secure the catheter over chest wall with micropore, or hold the catheter with a string, or contain it in cotton bag hanging over the neck

(B) Exit site care

1. Wash hands thoroughly
2. Inspect the site closely for signs of infection (redness, swelling, hotness, tenderness, discharge), swelling, skin excoriation, leakage, slippage, exposed cuff
3. Open the alcohol wipe/povidone-iodine swabstick pack 2% chlorhexidine gluconate carefully with fingers touch only the edge of the wipe/top of the swabstick
4. Cleanse the skin with the alcohol wipe/povidone-iodine swabstick/2% chlorhexidine gluconate starting from the exit site in a circular motion moving from the innermost to the outermost
5. Repeat the cleansing for at least three times with another pieces of alcohol wipe/povidone-iodine swabstick/2% chlorhexidine gluconate until a two-inch area around the exit site has been wiped including upper part of the catheter
6. Allow the alcohol/povidone-iodine/2% chlorhexidine gluconate to air dry and no dressing is needed if the skin of the exit site is normal
7. If stitch(es) on, exposed cuff or signs of infection over the exit site:
   - Perform the cleansing steps as from 4 to 6 using povidone-iodine swabstick/2% chlorhexidine gluconate
   - Allow to air dry
   - Apply semi-occlusive dressing
   - Secure the catheter as mentioned
8. Inform physician of any abnormality detected

(C) Catheter flushing

1. Flush all catheter lumens at least once weekly
2. Prepare items for catheter flushing (2-lumens):
   - 10 mL syringe × 6, Luer lock plug × 2, alcohol prep 10 mL, NS × 2, 50 units/5 mL HS × 2
3. Wash hands with soap and water thoroughly
4. Open the cap of HS
5. Disconnect the 10 mL syringe cap
6. Draw 5 mL HS into a 10 mL syringe
7. Repeat 4 to 6 on another 10 mL syringe with HS
8. Ensure the catheter clamp is closed
9. Take out the alcohol prep carefully
10. Swab the junction (catheter with luer lock plug) and end one inch of the catheter thoroughly with friction for at least 3 times with a new alcohol wipe one at a time
11. Disconnect the luer lock plug

Table 6 (*continued*)

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Table 6 (*continued*)

12. Swab the hub with friction for at least 3 times with a new alcohol wipe one at a time
13. Connect a 10 mL empty syringe onto the catheter hub
14. Release the catheter clamp
15. Aspirate 5 mL blood for discarding
16. Close the clamp
17. Fit a 10 mL syringe with 10 mL NS to clear the catheter with a push-pause technique (i.e., inject 1 mL, pause, inject another 1 mL, pause, etc.)
18. Close the clamp
19. Connect with 5 mL HS (50 units) and clamp the catheter when the plunger reaches the last 0.5 mL HS in syringe
20. Remove the syringe
21. Swab the hub thoroughly with alcohol wipe
22. Apply a new luer lock plug
23. Repeat step 8 to 22 to another lumen
24. Secure the catheter legs over chest
25. Any signs of catheter blockage:
    - Cannot withdraw any blood: do not force the irrigants into the lumen but plug the lumen after swabbing with alcohol wipe and then inform doctors or nurses
    - Can withdraw blood but not adequate or with resistance: continue the flushing procedure and inform doctors or nurse afterwards

(D) Complications monitoring and management

1. Catheter break or leakage
    - Clamp the catheter with non-toothed forceps as close to the skin as possible and seek medical aid
2. Catheter slippage
    - Secure central venous catheter/control bleeding and seek medical aid
3. Catheter slipped out:
    - Try to stop bleeding over entrance/exit site and seek medical aid
4. Edema of limb of the same side of the catheter:
    - Ensure the clamp is closed and seek medical aid immediately
5. Chest pain and cyanosis
    - Close the catheter clamp, lie on left side with head down
    - Seek medical aid immediately

HS, heparinized saline; NS, normal saline.

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Supplementary

Table S1 PubMed search strategy

#	Query
1	((supportive care[Title]) AND (hematopoietic[Title/Abstract])) OR (transplant[Title/Abstract])) OR (neoplasm[Title/Abstract])) OR (cancer[Title/Abstract])) OR (leukemia[Title/Abstract])) OR (leukaemia[Title/Abstract])) OR (lymphoma[Title/Abstract])) OR (myeloma[Title/Abstract])) OR (bone marrow[Title/Abstract])) OR (BMT[Title/Abstract])) AND ((“2001/01/30”[Date - Create] : “2022/06/30”[Date - Create]) Filters: English; Adults: 19+ years; Aged :65 +year
2	((symptom management[Title] AND (pain[Title] AND (anorexia[Title] AND (fatigue[Title])AND (pruritus[Title] AND (depression [Title] AND (anxiety[Title] AND (end of life[Title]) OR (guideline[Title]) OR (recommendation[Title])) AND (hematopoietic[Title/Abstract])) OR (transplant[Title/Abstract])) OR (neoplasm[Title/Abstract])) OR (cancer[Title/Abstract])) OR (leukemia[Title/Abstract])) OR (leukaemia[Title/Abstract])) OR (lymphoma[Title/Abstract])) OR (myeloma[Title/Abstract])) OR (bone marrow[Title/Abstract])) OR (BMT[Title/Abstract])) AND ((“2001/01/30”[Date - Create] : “2022/06/30”[Date - Create]) Filters: English; Adults: 19+ years; Aged: 65 +year

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