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WHAT'S NEW IN INTENSIVE CARE

Top ten tips for the management of critically ill hematopoietic stem cell transplantation recipients

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Hematopoietic stem cells are capable of self-renewal and have the outstanding property of giving rise to all blood and immune cells in a stable manner. Autologous and allogeneic therapeutic use of these cells has become a standard of care for various malignant and non-malignant hematological diseases. Both procedures are associated with a high level of medicalization, drug prescription, intra-hospital transfer, and ICU use. We sought to put forward ten important tips for the management of critically ill hematopoietic stem cell transplant (HSCT) recipients.

1. Autologous and allogeneic HSCT are different treatments

Autologous HSCT has no therapeutic effect per se but can overcome the prolonged cytopenia related to marrow suppression induced by the therapeutic use of high dose chemotherapies. Toxicities of high dose alkylating agents, cytarabine, and/or total body irradiation are responsible for most of the severe toxic and infectious complications after auto-HSCT. The clinical picture is either represented by chemotherapy-related toxicity (acute arrhythmia or bladder hemorrhage after alkylating agent, cerebellar or lung toxicity after cytarabine, severe mucositis or enterocolitis after total body irradiation) or by febrile neutropenia and sepsis. A retrospective analysis of 532 auto-HSCT recently showed that septic shock, mostly from the gastrointestinal (GI) tract, was the leading cause of ICU admission [1]. At experienced centers, less than 10% of auto-HSCT require ICU admission [2]. The pattern of organ dysfunction is clearly different to what is encountered in allo-HSCT. Studies reporting a mixture of both HSCT types should be interpreted with caution.

2. Allogeneic HSCT leads to more severe critical illness

Allo-HSCT is mostly used as an immunotherapy in hematological cancers. The conditioning regimen variably provides myelosuppression and immunosuppression. Also various sources of stem cell and wider donor type can be used with mitigation of the risk. Allo-HSCT is performed for high-risk acute leukemia in half of cases. Allo-HSCT is now frequently offered to older and frailer patients [3]. Up to 20% of allo-HSCT recipients develop life-threatening complications [3–6]. Acute kidney injury occurs in one-third of patients [4], highlighting HSCT toxicity. Consequently, ICU admission should be ideally thought about and discussed with patients early in the process. Early communication between ICU and transplant teams ahead and during the management of critical conditions is encouraged and most probably improves survival [7, 8].

3. HSCT techniques have little impact on life-threatening complications

Lower intensity conditioning regimen have allowed reduced toxicity rates, and a decrease in neutropenia-related infections [9], with reduced incidence of gram-negative bacteremia and invasive fungal infections. However, reduced intensity conditioning did not affect ICU admission rate or mortality [5, 10].

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4. The number and extent of organ dysfunction are the major determinant of death

Organ failure mostly arises sequentially with compensated changes in vital parameters until irreversible multiple organ failure (MOF). Early admission of patients with only one organ failure, chiefly acute respiratory failure or hemodynamic instability, can be beneficial in the HSCT population, whereas attempt to resuscitate MOF mostly fails [5, 7, 11]. SCT specialists should be trained to evaluate for compensated physiological derangement (i.e., heart and respiratory rates, creatinine level, delirium etc.). Also, assessing benefits from rapid response teams in this setting is warranted.

5. Clinical syndromes are not specific

Severe organ dysfunction commonly affects allo-HSCT recipients. Even though infection is the rule, several non-infectious complications can mimic sepsis. Pulmonary edema, engraftment syndrome, diffuse alveolar hemorrhage, sinusoidal obstruction syndrome, and posterior reversible encephalopathy are examples of life-threatening complications that can present with unspecific symptoms. In the case of acute respiratory failure, these complications occur at different times after allo-HSCT. Also, an extensive non-invasive diagnostic panel is justified to best decipher this spectrum as failure to identify etiology of pulmonary involvement is deleterious in this population [12, 13].

6. Opportunistic infections are common in allogeneic HSCT recipients

Infections result from delayed immune reconstitution and immunosuppression related to graft versus host disease (GVHD) prevention and treatment. As a consequence, the severity of opportunistic infection is not independent of GVHD [14, 15]. Diagnostic algorithms are lacking, especially in invasive filamentous fungi. Invasive procedures are more challenging. Finally, a careful review of past and present anti-infectious agents and other drugs that the patient received as well as the bioclinical picture analysis and timing regarding HSCT are mandatory to generate sound diagnosis hypotheses. In patients who are recipients of allogeneic HSCT, antifungal and anti-HSV prophylaxes have contributed to reducing transplantation-related mortality [9]. However, no antibacterial prophylaxis has demonstrated survival benefits unless patients present with febrile neutropenia.

7. Graft versus host disease is a major determinant of mortality

Acute GVHD is a major determinant of death in allo-HSCT recipients. This is a protean syndrome that leads to systemic inflammation, endothelial dysfunction, and organ dysfunction. Acute GVHD (aGVHD) leads to incremental immunosuppression and opportunistic infections as well as performance and nutritional status degradation. Studies reported a 70% mortality rate in aGVHD patients requiring life-sustaining therapies [5, 6]. In patients with controlled or stabilized aGVHD, a time-limited trial of ICU management should be offered to these high-risk patients. In patients with aGVHD unresponsive to treatments, tissues damages and organ failures become irreversible. In our experience, any attempt to provide life-sustaining therapies remains unbeneficial to patients, and palliative care should be implemented or intensified.

8. The ICU doors are widely open to the vast majority of HSCT recipients

In patients presenting with life-threatening complications after auto-HSCT or in allo-HSCT recipients without GVHD, ICU management should be prompt and unrestricted as these patients mostly have controlled malignancies and substantial long-term survival. ICU admission should also no longer be regarded as a binary decision. Apart from life-sustaining therapies, ICU is commonly a place with a higher nurse/patient ratio, easier access to safe diagnostic procedures, as well as habits relating to organ failure recognition. Early assessment of the goals of care for every patient help align expectations with those of the patients and ensure that critical care management is in line with her/his preferences [7]. For instance, in patients with no GVHD or when GVHD is in remission, a full code of ICU management should be offered. In patients with active but controlled aGVHD, a time-limited trial of ICU management might be appropriate. However, in patients developing acute respiratory failure or sepsis while aGVHD is uncontrolled despite high dose steroids and additional immunosuppressors, ICU management is likely to be non-beneficial and the goals of care should be shifted from curative to palliative (Fig. 1).

9. ICU management is a bridge to cure: long-term survival is substantial

Evidence is now accumulating that intensive care has to be a part of many HSCT recipients' journey. In a retrospective longitudinal cohort of 330 ICU admissions out of 942 HSCT procedures, authors found that post-ICU survival was comparable between ICU survivors and patients never admitted to the ICU [16]. Performance status, quality of life, and functioning of ICU survivor should be studied in depth but seem reasonably reassuring in small series [17].

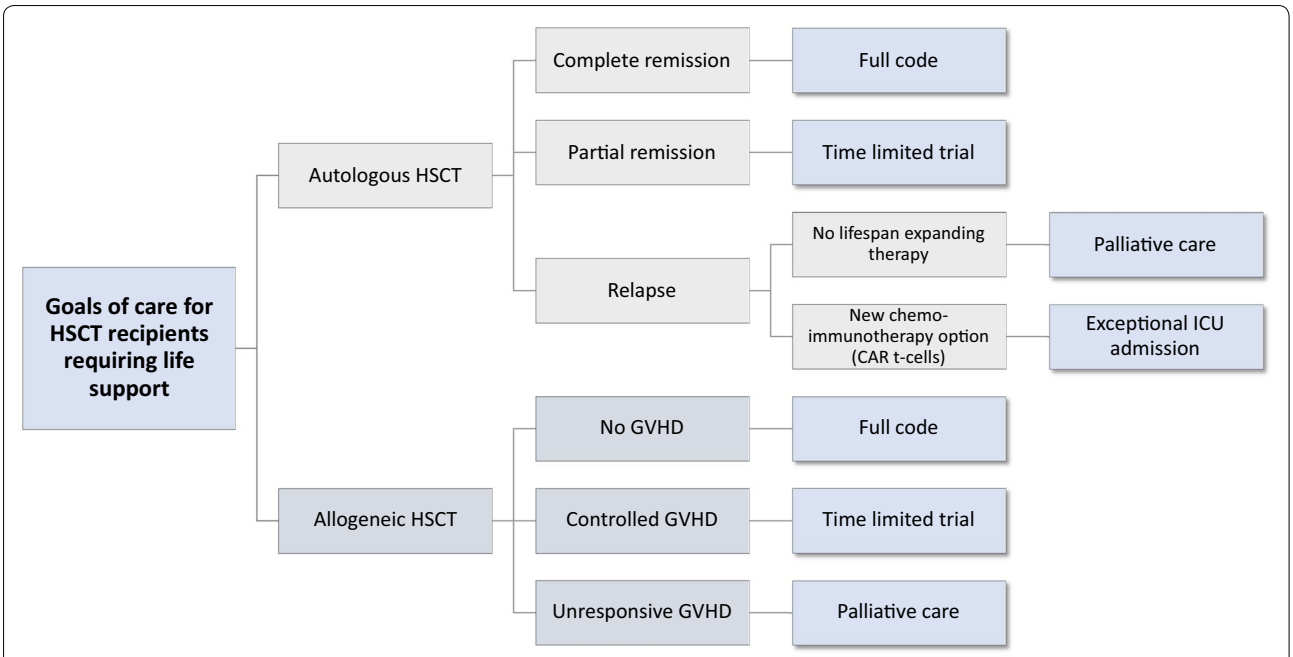

Fig. 1 Goals of care algorithm for HSCT recipients requiring life support

10. Future of the ICU and cell therapy interface

Immunotherapy becomes of paramount importance in onco-hematology. The recent release of various genetically modified allo or auto chimeric antigen receptor (CAR) T cell therapy will for sure change the HSCT landscape. Substantial response rates are reported in patients with refractory acute lymphoblastic leukemia (ALL) or B cell lymphoma receiving CAR T cell therapy, at the price of high rates of cytokine release syndrome and neurotoxicity. Infection is also a common finding in these high-risk patients. It is likely that a broader use of CAR T cell therapy will help in fine-tuning intensivist–hematologist relationships. On the one hand, these therapeutic advances include an ICU journey in 15–50% of the cases, making critical care specialists at the front line of modern hematology [18]. This includes assessment of a patient's eligibility for immunotherapy and HSCT, strategies to prevent severe organ dysfunction, and early ICU management. On the other hand, critical care specialists need to engage in exceptional ICU admission for patients with refractory hematological malignancies in whom new hopes are made available, and adjust the goals of care for those remaining unresponsive.

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Compliance with Ethical Standards

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