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RESEARCH AGENDA

The Intensive Care Medicine research agenda on critically ill oncology and hematology patients

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Abstract

Over the coming years, accelerating progress against cancer will be associated with an increased number of patients who require life-sustaining therapies for infectious or toxic chemotherapy-related events. Major changes include increased number of cancer patients admitted to the ICU with full-code status or for time-limited trials, increased survival and quality of life in ICU survivors, changing prognostic factors, early ICU admission for optimal monitoring, and use of noninvasive diagnostic and therapeutic strategies. In this review, experts in the management of critically ill cancer patients highlight recent changes in the use and the results of intensive care in patients with malignancies. They seek to put forward a standard of care for the management of these patients and highlight important updates that are required to care for them. The research agenda they suggest includes important studies to be conducted in the next few years to increase our understanding of organ dysfunction in this population and to improve our ability to appropriately use life-saving therapies or select new therapeutic approaches that are likely to improve outcomes. This review aims to provide more guidance for the daily management of patients with cancer, in whom outcomes are constantly improving, as is our global ability to fight against what is becoming the leading cause of mortality in industrialized and non-industrialized countries.

Keywords: Neutropenia, Bone marrow transplantation, Mechanical ventilation, Oxygen, Acute respiratory failure, Septic shock, Cancer, Bronchoscopy

Introduction

Cancer remains a leading cause of death in the general population, and the first cause of death in men and women over 40 years old [1, 2]. Significant medical progress has been achieved by means of more intensive chemotherapy regimens or hematopoietic stem cell transplantation (HSCT), targeted therapies in selected diseases with recurrent tumorigenic mechanisms, or adoptive cell transfer technology.

Overall, the cancer death rate has dropped by 23% since the 1990s, translating to millions of deaths averted. The American Association for Cancer Research recently reported that the number of cancer survivors increased from 1 in 69 (1.4%) to 1 in 21 (4.8%) people [1, 2].

Despite this progress, death rates from cancer remain substantial and challenging. In the years to come, accelerating progress against cancer will increasingly require

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intensive care unit (ICU) support with the use of life-sustaining therapies for infectious or toxic chemotherapy-related events [3]. With rapid development of new drugs, this phenomenon can only proliferate. For instance, the recent use of tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) to reverse cytokine-releasing syndromes in chimeric antigen receptor (CAR) T cell therapy associated with vascular leakage respiratory distress and refractory hypotension, has resulted in a greatly increased demand for life support measures over less than a decade [4].

Over the past two decades, five major changes have occurred: (1) the number of cancer patients needing ICU care has dramatically increased, with 15% of ICU beds occupied by cancer patients [5, 6]. (2) Survival has improved and is below 30% in the ICU and below 40% in hospital (Fig. 1). Moreover, at least for hematology patients, ICU survivors achieve remission and good quality of life as much as non-ICU patients [7, 8]. (3) Most classic predictors of mortality have lost much of their value [9]. (4) Non-invasive diagnostic and therapeutic strategies have allowed new clinical approaches for high-risk cancer patients [10]. These strategies have advocated early admission to the ICU, avoiding risky procedures, and offering earlier monitoring. (5) Finally, because triage criteria for ICU admission have shown poor reliability, new strategies of ICU admission have been offered to cancer patients [9, 11].

This group of authors includes experts in the management of critically ill cancer patients who have recently published on this topic. The literature review searched most relevant articles appearing in PUBMED since the year 2000. Earlier publications may have been quoted because they are used as landmark contributions to the field or as reference prior to major changes. In this review, we highlight recent changes in the use and the results of intensive care in patients with malignancies. In addition to describing the standard of care for the management of cancer patients, a research agenda includes important studies to be conducted in the next few years to increase our understanding of organ dysfunction in this population and to improve our ability to appropriately use life-saving therapies or select new therapeutic approaches that are likely to improve outcomes.

Current standard of care for critical care delivery to patients with malignancies

We all believe that it is mandatory to harmonize the level of care provided to cancer patients across countries, institutions, and ICUs [9, 12, 13]. The following elements of the standard of care have been developed in recent years and merit attention.

Avoiding delayed admission to the ICU

Initial reluctance to admit cancer patients to the ICU leads to repeated discussions, conflicts, and delayed ICU admission [14]. Bed availability is also an issue in some settings [15], and ICU treatments can be delivered outside the ICU [16]. However, admission to the ICU shortly after the start of the critical care illness is associated with better survival rates [8]. In patients with acute respiratory failure, both oxygen requirement at presentation and time between hospital and ICU admission have been shown to be associated with mortality [17]. Likewise, direct admission to the ICU leads to decreased mortality in patients with hyperleukocytic acute myeloid leukemia (AML) who are at high risk of tumor lysis syndrome and leukostasis but have no organ dysfunction at presentation [18]. Moreover, early detection of the physical changes that announce the onset of critical illness plays an important role in alerting clinicians that the time for ICU admission may have come [19]. In addition to a rapid response team, use of the Modified Early Warning Score (MEWS) or of biomarkers such as serum lactate has proven effective in enhancing prompt admission to the ICU [20].

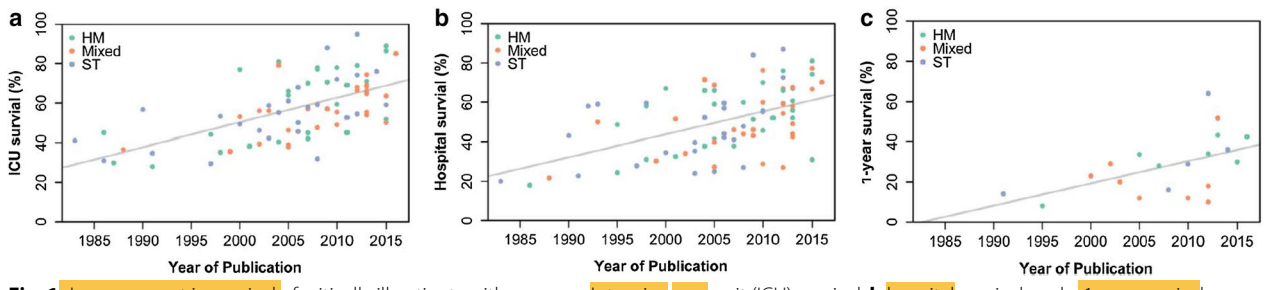

Fig. 1 Improvement in survival of critically ill patients with cancer. **a** Intensive care unit (ICU) survival, **b** hospital survival, and **c** 1-year survival are illustrated. The results shown are from publications that reported the survival of critically ill patients with cancer who required ICU admission. *Each dot* represents the mean survival reported in one study, and the *color of the dots* represents the patient population. *Green* studies reported the survival of patients with hematologic malignancies (HM), *blue* studies reported the survival of patients with solid tumors (ST), and *red* studies reported the survival of mixed populations, including patients with HM and patients with ST From Shimabukuro-Vornhagen et al. [3]

Diagnostic strategy in patients with acute respiratory failure

Acute respiratory failure (ARF) is the leading cause of ICU admission among patients with cancer [21]. As there are many possible ARF etiologies, a timely and accurate diagnostic strategy that takes into account characteristics of the underlying malignancy, the type of immune suppression, the type of respiratory symptoms, and radiological findings, as well as associated organ dysfunctions is appropriate [22, 23]. High-resolution computed tomography of the thorax provides important guidance for the choice of appropriate diagnostic tests [24]. Pleural and pulmonary echography, as well as echocardiography, are noninvasive tests with high diagnostic yield. Early fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) were the cornerstones of the diagnostic workup until a multicenter randomized controlled trial (RCT) reported that management with or without BAL led to similar outcomes [10]. Surgical lung biopsy has long been considered as the gold standard for identifying ARF etiology in cancer patients with pulmonary infiltrates; however, recent findings showed that the procedure was not superior to BAL for diagnosis of infections, while still associated with higher morbidity and mortality [25]. Beside the highly variable outcomes associated with the various causes of ARF (15% mortality in cardiogenic pulmonary edema and 85% in patients with invasive aspergillosis), inability to identify ARF etiology is an independent predictor of mortality [26].

Initial oxygenation strategy for acute hypoxemic respiratory failure

The literature is equivocal in terms of harm or benefit from noninvasive mechanical ventilation (NIV) in these patients. The need for invasive mechanical ventilation has been associated with mortality in numerous studies [27]. A recent trial from the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH) on early NIV in immunocompromised patients with hypoxemic ARF reported no significant benefits from NIV [28]. However, mortality has decreased significantly over the last decade [29–31]; it was 90% in the control group of Hilbert's trial [32], but only 26% in both groups of Lemiale's trial [28]. Half the patients with severe ARF and 75% of severe ARDS patients experience NIV failure with significantly higher mortality [33, 34]. Therefore, NIV may be used with caution in cancer patients with hypoxemic ARF, and should be avoided in severe hypoxemia. The five following elements strongly suggest that the literature is inconclusive and that trials are warranted: (1) early NIV does not translate anymore into survival benefits, and is maybe harmful; (2) high flow oxygen has demonstrated survival benefits as compared to NIV [35]; however, this is still controversial in cancer patients [36, 37]; (3) mortality has decreased in patients with severe ARDS and in non-ARDS patients receiving mechanical ventilation [38–40]. In a multicenter cohort of hematology patients admitted to 17 ICUs in France and Belgium [8], mortality among patients with ARF was 42%. (4) It is increasingly believed that NIV cannot avoid high tidal volumes being delivered to hypoxemic patients with high respiratory drives, and possible ventilator-induced lung injury and worsening of respiratory status [41]. (5) Last, most of the studies do not adjust for cofounders such as the ability to identify and treat ARF etiology.

Patients with malignancies are at high risk of severe pulmonary complications, including ARDS [42]. The disease can also occur in patients with neutropenia [43] or during recovery from neutropenia [44]. The use of the best standard of care in these patients [40] is associated with survival. Hospital mortality of cancer patients with ARDS has dropped to almost 50%, presumably owing to improved standards of invasive mechanical ventilation, development of proper diagnostic strategies, and early treatment of disease-related complications [10, 42, 45, 46]. NIV of severe ARDS cancer patients should be discouraged as it is associated with a high failure rate and increased mortality [33, 47].

Hemodynamics (fluids, vasopressors, monitoring)

The available data do not suggest specific needs of septic cancer patients with regard to fluid administration, vasopressors, or monitoring [48, 49]. Neither the macrocirculation (vasopressor dose and duration) nor the microcirculation (flow heterogeneity) seems to be impacted by neutropenia or chemotherapy [50, 51]. In patients with hyperleukocytic leukemia and leukostasis, increasing the hematocrit by transfusions disturbs rheology and end-organ perfusion and leads to life-threatening hyperviscosity. Hydration is recommended using saline at a volume of 30 ml/kg/day. Otherwise, the usual standard of care for managing hemodynamics should apply [52–55].

Acute kidney injury and renal replacement therapy

Acute kidney injury (AKI) occurs in up to 70% of critically ill cancer patients, half of whom need renal replacement therapy (RRT) [56, 57]. Sepsis, hypoperfusion, and nephrotoxic agents are the main leading factors [56, 57]. A few unique causes may, however, require specific management (Table 1). Early ICU admission has been associated with better renal and overall patient outcome [9], which probably relates to preventable causes of AKI such as tumor lysis syndrome or sepsis [58]. Cancer patients who are profoundly thrombocytopenic are at high risk of hemorrhage; thus, systemic anticoagulation may be

Table 1 Causes of AKI requiring specific management in oncology and hematology patients

Cause	Context	Basis of management
Tumor lysis syndrome	High-grade hematological malignancy	Hydration, recombinant urate oxidase, prophylactic RRT Avoid alkalinization; beware diuretics
Methotrexate (MTX) intoxication	High-dose MTX Possible occurrence after low-dose/oral MTX	Hydration, alkalinization, avoid interactions[a], leucovorin, glucarpidase
Myeloma cast nephropathy	Hypovolemia or sepsis, aciduria, hypercalcemia	Hydration, initiate myeloma treatment, treat favoring factor High-cutoff membrane RRT under evaluation
Infiltration	Mainly hematological malignancies (lymphoproliferative disorders)	Chemotherapy
Obstruction	Solid tumors and bulky lymphoma	CT- or echo-guided urine derivation (percutaneous nephrostomy). JJ stent or nephrostomy, initiate chemotherapy
Disseminated intravascular coagulation	Acute myeloid leukemia (AML3++), disseminated metastatic malignancy	Plasma transfusion, treatment of underlying malignancy

[a] Antifolate agents: cotrimoxazole; drugs interacting with MTX protein-binding: aspirin or nonsteroidal anti-inflammatory drugs; drugs interacting with biliary or urinary excretion of MTX: piperacillin-tazobactam, proton pump inhibitors

avoided by using either citrate or RRT without anticoagulation [59].

Transfusion strategies

Red cell transfusions should be implemented with caution in plasmatic (Waldenström disease or multiple myloma with high paraproteinemia) or cellular hyperviscosity (hyperleukocytic leukemia) for rheological reasons. In these cases, anemia should be tolerated as much as possible.

In unselected patients, a restrictive red blood cell (RBC) transfusion policy to maintain a hemoglobin level above 7 g/dl can be implemented in critical conditions in the ICU in otherwise hemodynamically stable patients. Presumably this may also apply to cancer patients. A large multicenter RCT in patients with septic shock reported that such an approach was safe, although it did not specifically address the optimal transfusion threshold in the event of persistent tissue dysoxia [60, 61]. In cancer patients following major surgery, a single-center RCT suggested benefit from a higher transfusion threshold [62].

Platelet management strategies are derived from studies performed in patients with hematological cancer in whom the risk of major bleeding is related mainly to the depth and duration of thrombocytopenia: prophylactic platelet transfusion at a threshold of 10×10^9/l is associated with less bleeding than therapeutic-only platelet transfusion [63, 64]. However, the link between thrombocytopenia and bleeding is unclear in the critically ill hemato-oncological patients where platelet aggregative functions and vascular integrity may also be altered. Therefore, additional studies are required to clarify the indications and thresholds for platelet transfusion in these patients. Granulocyte transfusion has become anecdotal.

Antibiotics and antifungals

Antibiotic and antifungal therapy is at the core of critical care of cancer patients, but its effectiveness is threatened by increasing resistance and faltering development of new drugs. Multidrug resistance is ubiquitous. Recent updates have included the advice to tailor empirical schemes to local ecology [3, 5], to restrict dual Gram-negative and anti-MRSA empirical coverage to specified patient risk categories [65, 66], and to de-escalate in patients with susceptible pathogens and clinical stabilization [67].

Hematology versus oncology: the main differences

While up to 15% of patients with a hematological malignancy will require admission to ICU [7], the majority of ICU cancer patients have solid tumors. One in 20 patients with a solid tumor will require admission to ICU within 2 years of diagnosis [68, 69], and they account for 85–93% of the ICU cancer workload (most are elective postoperative patients) [70]. In contrast, patients with hematological malignancies are more likely to be admitted to the ICU because of a medical condition, with high severity of illness scores and poorer outcomes as a result [8, 71]. Other striking differences include the small number of critically ill patients with solid tumors who are medical (as compared to scheduled surgery), profoundly neutropenic, or present with invasive fungal infection. Similarly, compared to patients with acute leukemia or lymphoma, chemotherapy is rarely given to patients with

solid tumors in the ICU. While the demographics may be different, short-term survival in both solid tumor and hematological malignancy patients has been consistently demonstrated to be related to the severity of illness rather than the underlying malignant diagnosis [72]. However, performance of physiologic scores is poor in cancer patients. Instead, severity of organ dysfunction, at admission and throughout the ICU stay, is associated with mortality.

Major recent advances in the field

Advances outside the ICU

A medical emergency team (MET) takes critical care expertise wherever it is needed to prevent morbidity or mortality. MET activation is indicated when a staff member is worried about a patient. MET implementation is associated with reductions in both hospital mortality and non-ICU cardiopulmonary arrests [73–76]. Last, studies have shown that in patients undergoing surgical procedures, protective lung ventilation during anesthesia translates into reduced complication rates and decreased ICU admissions.

ICU organization

Optimization of ICU organization and processes of care is paramount in the face of increasing demands and costs to provide high-quality and affordable critical care to a growing population of patients living with cancer. Improved outcomes were observed in patients transferred from the wards to the ICU early in the course of an acute illness [8, 17, 18, 77] and in those admitted to ICUs run by intensivists [78]. In a recent multicenter study, daily formal meetings between the attending hematologist/oncologist and intensivist for the purpose of care planning and the implementation of protocols were associated with lower mortality rates and more efficient resource use [6]. Mortality was also lower in ICUs with clinical pharmacists and multidisciplinary teams [6].

Sepsis management

Several studies have reported improved survival rates in cancer patients with septic shock. It is noteworthy that such improvements have appeared more pronounced in the most vulnerable populations, such as patients with malignancies [79, 80], although the current management of septic shock in cancer patients is largely derived from interventional studies in which they were underrepresented [52, 81]. This may be attributable to early recognition of sepsis and rapid implementation of sepsis bundles. Furthermore, some observational studies have delineated areas of improvement in neutropenic sepsis, including escalation and de-escalation principles for antimicrobial management, source control including catheter removal in the absence of an alternative focus of infection, and the feasibility and safety of surgery in neutropenic patients even if thrombocytopenic [45, 82, 83]. In the absence of prospective interventional studies in critically ill neutropenic patients, indications for adjuvant G-CSF treatment to shorten the duration of neutropenia remain elusive [84]. G-CSF-enhanced deterioration of respiratory status at the time of recovery from neutropenia is a concern in patients with pulmonary involvement [85–87]. Importantly, some aggressive malignancies may manifest as sepsis-like syndromes with multiple organ failures. In these situations of hemophagocytic lymphohistiocytosis (HLH) or severe tumor lysis syndromes, emergent chemotherapy treatment is started in patients receiving life-sustaining therapies [58, 88–90].

Chemotherapy (for selected ICU patients with newly diagnosed malignancies)

Data from cohort studies suggest that providing cancer chemotherapy along with life-sustaining therapies in critically ill patients with cancer-related organ dysfunctions (organ or vessel compression, tissue infiltration, tumor lysis syndrome, etc.) is feasible and associated with a meaningful survival benefit in selected patients [91–93]. Patients' preferences, performance status, and associated comorbidities, together with the availability of life-span-expanding treatment, need to be carefully assessed in close cooperation with the attending oncologist or hematologist [91–93]. Associated sepsis or need for life support at the time of chemotherapy onset should not be seen as a contraindication to chemotherapy. However, major concerns related to administration of chemotherapy in the ICU lie in the practical management of antineoplastic drugs by teams with little experience. Dedicated protocols, routine prescription by specialists, daily rounds with hematologists and oncologists, and careful identification and securing of the medication circuit, ideally with the help of a clinical pharmacist, are needed to ensure safe delivery of chemotherapy in critically ill patients [6]. Nurse consultants from the hematology/oncology wards who are familiar with administrating chemotherapy may also provide precious help.

Common beliefs contradicted by recent findings

The landscape of the management of critically ill patients with cancer has changed dramatically over the past 15 years (Table 2). Intensivists' skills in understanding the pathophysiology of several diseases, awareness of the risk associated with neutropenia, management of urgent complications related to the malignancy, and their ability to start chemotherapy while providing advanced supportive care have all significantly improved. As a consequence, some concepts should be revised.

Table 2 Recent changes to previously held beliefs pertaining to the management of critically ill cancer patients

1. It is wrong to state that cancer-related characteristics (e.g., type of cancer, neutropenia, cancer-related complications) are the main prognostic factors among the pre-acute illness conditions
2. It is wrong to state that de-escalation of antibiotics is unsafe in neutropenic patients with septic shock
3. It is wrong to state that FOB-BAL is mandatory in the diagnostic workup of patients with ARF and pulmonary infiltrates
4. It is wrong to state that noninvasive ventilatory support strategies should be the rule in patients with ARF, as they improve survival and reduce intubation rates
5. It is wrong to state that our ability to identify patients likely to benefit from ICU admission or not is optimal
6. It is wrong to state that prognostic scores can assist in ICU admission triage decisions
7. It is wrong to state that intensivists and oncohematologists should plan care separately to avoid conflicts
8. It is wrong to state that outcomes in high-volume centers are the same as in general hospitals
9. It is wrong to state that one should wait for resolution of organ failure before starting chemotherapy
10. It is wrong to state that the ICU is not the place for palliative care and should be restricted to cancer patients with full-code status

FOB-BAL fiberoptic bronchoscopy with bronchoalveolar lavage, *ARF* acute respiratory failure, *ICU* intensive care unit

Cancer-related characteristics are no longer associated with short-term mortality

For decades, the diagnosis of malignancy per se and complications from underlying disease or its treatment drove decisions to offer critical care to cancer patients. Over the past 20 years, we have learned that the nature and the staging of the underlying malignancy are no longer associated with mortality after an ICU stay [9, 11, 70, 72]. Indeed, for cancer patients selected by oncologists/hematologists, disease-related characteristics do not affect outcomes. Also, the impact of the underlying disease is erased by mechanical ventilation, vasopressors, or RRT. With the increasing use of time-limited trials, however, patients will be selected chiefly on the basis of their performance status, but also their ability to receive high-dose therapy, challenging the impact of cancer characteristics on outcome [8, 94, 95]. Finally, at a time when targeted therapy and biotherapies are widely used in cancer patients, it is likely that an increased number of patients with advanced disease will be admitted to the ICU, warranting a reappraisal of classic predictors of mortality [3].

Performance status is a constant predictor of mortality

Performance status (PS) is a simple and widely used scale to assess function and guide treatment in patients with cancer. It is a key outcome predictor in all critically ill patients [8, 9, 11, 70, 96]. Altered PS may be related to the burden of age and comorbidities, or to the aggressiveness of the disease. Whatever the reason why PS is altered, studies have shown that poor PS translates into increased mortality, with case fatality reaching 85–90% in patients who are bedridden or dependent [8, 9, 11, 70, 96].

Neutropenia is probably not a predictor of high mortality

Until the early years of this century, neutropenia was considered to be associated with very high mortality in the critically ill, leading to the common belief that life-saving therapies were futile in these patients. However, advances in the management of specific complications in patients with neutropenia, the diagnosis and management of infections, and the routine use of prophylactic antibiotics and antifungals based on updated recommendations have been substantial [9, 45, 67, 97]. We do not recommend including neutropenia as a driver for admitting or not admitting a patient to the ICU. Similarly, we do not recommend that neutropenia be taken into account in deciding to withhold or withdraw life-sustaining therapies [98]. In this setting, studies to confirm safety and feasibility, and also the potential individual or collective benefits of de-escalation in patients with neutropenia, are warranted [99].

Not every patient with acute respiratory failure and pulmonary infiltrates should undergo fiberoptic bronchoscopy and bronchoalveolar lavage (FOB-BAL)

Hypoxemic acute respiratory failure with pulmonary infiltrates is one of the major life-threatening complications in patients with hematological malignancies. Management of these patients is complex, and failure to identify the cause of ARF is associated with poor outcomes [26, 42]. FOB-BAL was considered as the cornerstone of the diagnostic strategy in this setting. However, respiratory deterioration and the need for intubation following BAL have been reported [100]. Mandatory FOB-BAL was challenged by a multicenter randomized trial, the results of which suggested that an initial noninvasive diagnostic strategy (based on sputa, nasopharyngeal aspirates, blood, urine, or imaging tests) without FOB-BAL may be safe and effective in most patients [10]. Compared to FOB-BAL, noninvasive tests have the same diagnostic and therapeutic yields. However, 15% of the patients still require FOB-BAL, chiefly those with suspected *Pneumocystis* pneumonia, with drug-related

pulmonary toxicity, or who present possible drug-related pulmonary toxicity. We advocate that expert discussion should be performed prior to any diagnostic tests, as the clinical relevance of the results relies on the pretest probability of every single potential diagnosis. Notably, some vignettes can only be made using BAL (alveolar hemorrhage, alveolar proteinosis, etc.). Finally, we recommend that patients undergoing lung biopsy for diagnostic purposes first undergo FOB-BAL. A personal approach tailored to every patient according to the underlying disease, ongoing prophylaxes and treatments, as well as local facilities to perform all possible noninvasive tests or to secure and optimize FOB-BAL are required.

ICU triage and admission policies

Obviously, every medical decision must emphasize justice (a chance for all according to what is available) and autonomy (values and preferences of patients). We know that decision-making with regard to ICU admission is imprecise and that this is a source of increased mortality owing to delayed ICU admission, as well as a source of nonbeneficial care [101, 102]. In cancer patients, all these elements are valid and even translate into higher attributable mortality [103]. In a single-center study, one in four patients considered by the ICU team to be too sick to benefit from ICU admission actually survived, while one in five patients considered too well to benefit actually died [103]. In addition, we cannot rely on severity of illness scores to guide a decision at the level of the individual patient. As our ability to identify cancer patients likely to benefit from ICU management is limited, new strategies of ICU admission have been developed and validated (Fig. 2) [95, 104–106]. Time-limited trials [95, 105] have been one of the major changes with regard to ICU admission of cancer patients since the turn of the century. The strategy consists in unlimited ICU management with a full-code status for a limited period. Patients and relatives are important partners in all decisions. The time of full-code status seems to be at least 2 weeks in hematology patients, unless they are in multiple organ failure, in which case 1 week would be enough to provide the same survival as with unlimited aggressive care [95, 105]. In patients with solid tumors, a week of ICU trial should be enough, and in the case of multiple organ failure, a full-code management for 4–5 days leads to similar outcomes as unlimited aggressive care [95, 105]. The impact of identified targets for biotherapy is not known [107]. Other strategies of ICU admission include prophylactic ICU admission in patients at high risk for tumoral compression, lysis syndrome, leukemic infiltrates, etc. These new strategies of ICU admission have been widely accepted for patients with hematological malignancies and are recommended in guidelines published by the British Committee for Standards in Hematology and

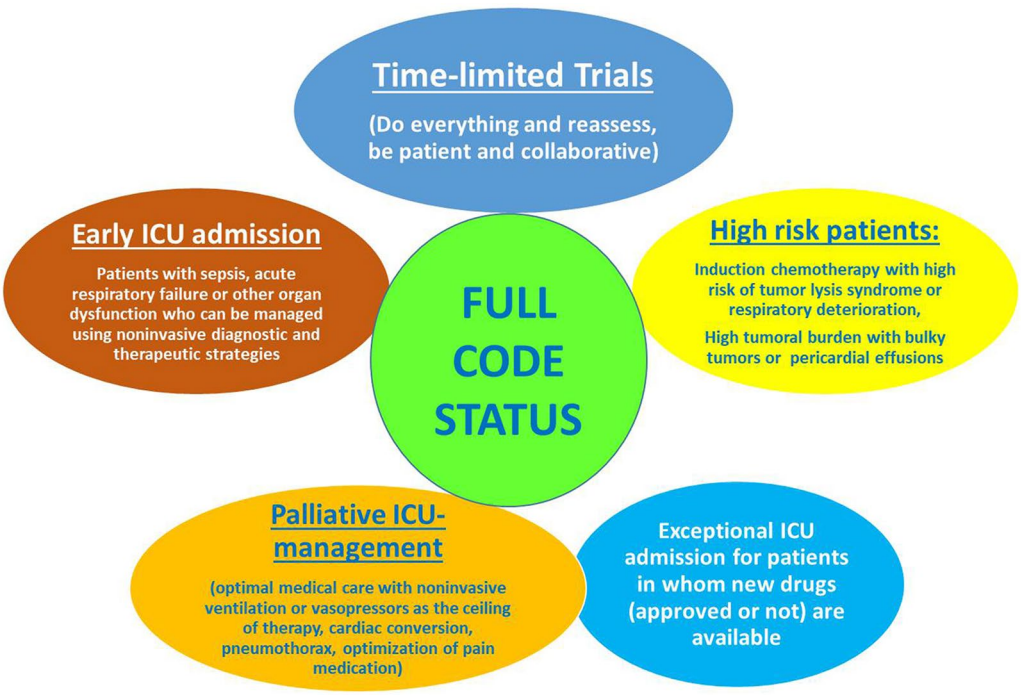

Fig. 2 New strategies of ICU admission in patients with cancer

in French guidelines [67, 108]. Importantly, in settings where bed availability is limited, early aggressive treatment can be initiated outside the ICU [16].

Collaboration between hematologists/oncologists and intensivists

Care of critically ill patients with cancer is complex and multifaceted. Experts have recommended close collaboration among intensivists and oncologists/hematologists [6, 9, 11]. On the one hand, ICU physicians are skilled in managing organ dysfunctions and setting goals for life-sustaining interventions. On the other hand, hematologists and oncologists can discuss with them the pathophysiological aspects of malignancies and related complications, possible toxicities, new therapeutic options, and the potential for cure and outcomes regarding the underlying malignancy [6, 11]. One good example is provision of urgent chemotherapy in the ICU for selected patients with highly proliferative malignancies and associated acute organ failures [91–93]. In the ORCHESTRA study, a multicenter study involving almost 10,000 admissions to 78 ICUs, meetings between oncologists and intensivists for care planning and setting of goals on a daily basis led to lower mortality and more efficient resource use [109]. To further highlight the need for a multidisciplinary team approach, survival was also lower in ICUs with clinical pharmacists [6].

Palliative care and critical care are not mutually exclusive

For a long time, palliative care in the context of a critical illness was only considered in patients at the end of life. In recent decades, we have learned that integrating palliative care for critically ill patients is mandatory, can be introduced early and last for long, regardless of their prognosis [110]. High-quality palliative care includes optimal symptom control, communication about appropriate care goals, and support for both patient and family throughout the illness trajectory [72]. Although we should prioritize ICU admission for patients with full-code status and those suitable for an ICU trial, we have also learned that some selected patients can be admitted for noninvasive strategies and supportive care [104, 106]. Along this line, one of the five principles of Choosing Wisely Campaign Guidelines related to the use of palliative care as an option for every critically ill, not only at their terminal phase (http://www.choosingwisely.org/interdisciplinary-critical-care-societies-identify-five-common-clinical-practices-to-reconsider/).

Remaining areas of uncertainty

Long-term outcomes

The current paradigm shift in considering cancer patients for intensive care is mainly based on markedly improved shorter-term outcome indicators such as mortality (in the ICU, in hospital, or within 30–90 days). While important in their own right, these endpoints may be too limited to permit valid conclusions as to the actual benefits and overall cost-effectiveness of ICU care in cancer patients. However, data on long-term survival after critical care management and functional outcomes, such as QOL or post-ICU burden (depression, anxiety, and post-traumatic stress disorder), are scarce in cancer patients.

Some 15 years ago, the 1-year survival rate of mixed hematologic and oncologic ICU patients was about 25% [72]. More recent studies report higher but quite variable 1-year rates ranging from 18% to 64% [7, 8, 92, 111, 112]. In a large prospective multicenter study of 1011 hematologic patients admitted to 17 French and Belgian centers, the 1-year survival rate was 43% [8]. A few smaller studies, e.g., in patients with acute myeloid leukemia, diffuse large B cell lymphoma, highly aggressive non-Hodgkin lymphoma, chemotherapy during the ICU stay, or post allogeneic hematopoietic stem cell transplant reported survival rates beyond 1 year: 2-year survival ranged from less than 20% to 50% [7, 46, 92, 111, 113]. The most significant advance regarding long-term outcomes was achieved by Schellongowski et al. in a retrospective single-center study on AML patients in Vienna [7]. Among the patients alive 30 days after ICU admission, overall survival, disease-free survival, and the proportion of patients with complete remission did not differ significantly between patients who needed ICU management and those who never did [7]. Up to 80% of ICU survivors actually continue standard optimal chemotherapy and are in remission 6 months after ICU discharge [8]. Corresponding data on patients with solid tumor are sparse, but they are expected to vary according to type of tumor [68, 114]. In lung cancer patients, the initial anticancer treatment plan required reduction or modification in 38% of ICU survivors, mostly dependent on the previous performance status [115]. In general, long-term survival of ICU survivors seems to be largely independent of severity of illness and characteristics of the ICU stay (i.e., the main determinants of ICU and hospital mortality): instead, cancer prognosis correlates with post-ICU survival [7, 46, 72, 92, 111, 113, 116].

In a study surveying cancer patients 18 months after admission, health-related QOL was similar between hematologic patients who needed ICU management and those who did not [98, 117]. In a cohort of cancer patients chiefly including solid tumors, markedly reduced QOL 1 year after ICU discharge was reported [112]. It is noteworthy, however, that more than 90% of patients prefer to be readmitted to an ICU in the event of a new deterioration [112]. A recent Brazilian study on elderly ICU patients with mainly advanced oncological malignancies

found a probability of only 30% and 19%, respectively, for attaining 12 and 18 months of quality-adjusted survival. The authors identified a series of baseline characteristics, among them performance status, QOL prior to ICU, performance status, and cancer and therapy status, which strongly correlated with QOL after 18 months [114].

The ICU may offer the best possibilities for effective pain and symptom management [110, 118, 119]. However, studies highlight that bereaved families perceive and recall the patient's last days or weeks as suboptimal [120]. We do not recommend the use of ICU services for dying patients.

The 10 most important studies/trials in the next 10 years

A lot remains to be done to further reduce mortality in cancer patients requiring life-saving interventions (Table 3; Fig. 3). We identified the following domains to be evaluated in more depth, and suggestions for future research are provided below.

Early ICU admission

There is a need to develop specific early warning scores to predict clinical changes in high-risk patients (myeloablative treatment for HSCT or induction chemotherapy for AML) [121, 122]. Since respiratory failure and sepsis are the principal indications for ICU admission of cancer patients, respiratory rates, oxygen saturation, hypotension, mental status, and tachycardia are the main parameters to be monitored for early detection. The role of biomarkers is currently unclear in this specific group of patients. Innovative technology (wireless devices, e-tools) appears promising and its use needs to be investigated. In the future, according to healthcare models and to countries, it is possible that no ICU bed will be available for early ICU admission. Then, studies will be needed to demonstrate that treating these patients in the ward is not saving cost as compared to early ICU admission.

Alternatives to intubation in cancer patients with acute respiratory failure

Noninvasive mechanical ventilation (NIV) and high-flow oxygen therapy (HFNC) have proven effectiveness to reduce intubation in cancer patients with acute hypoxemic respiratory failure but no indications for intubation [32, 35, 36]. HFNC may have both helped to improve outcomes and raised concerns about NIV [9, 26, 35, 36, 123]. However, conflicting data have been published, with no impact of NIV as compared to oxygen in Lemiale's trial and harmful effect of NIV as compared to HFNC in Frat's trial [28, 36]. However, Mokart et al.'s retrospective study [124] found no excess mortality with HFNC+NIV. Noteworthy, both the Frat and Lemiale's trials have been criticized for the lack of optimal NIV delivery. Indeed, in these trials the proportion of patients receiving more than 12 h of NIV per day did not exceed 20%. Also, in the post hoc analysis of Lemiale's trial, HFNC was not associated with any survival benefits [37]. Confirmatory data are needed to prove benefits of HFNC in immunocompromised patients. To date, no study has evaluated NIV versus intubation in patients meeting the indications for intubation as performed in unselected patients [125]. A study where NIV/CPAP would be evaluated as an alternative to mechanical ventilation in patients with indications for intubation is warranted, especially for cancer patients with ARDS. Here, NIV delivery would be guided by close respiratory monitoring and physiological evaluation such as transpulmonary pressures, ventilator-induced lung injury (by monitoring expiratory tidal volume), and work of breathing.

Future of diagnostic strategies for infection

Diagnosis of infection and of its resolution based on routine clinical, biochemical, and radiological signs is inaccurate in cancer patients. Standard microbiological workup increases specificity at the cost of longer time to diagnosis, whereas empirical antimicrobial therapy is challenged

Table 3 Ten major challenges critical care specialists will face with cancer patients in the next 10 years

1. Increasing numbers both of patients diagnosed with cancer and of cancer survivors
2. Increasing need for ICU management of cancer patients due to intensive therapeutic regimens and highly toxic targeted therapies
3. Increasing number of cancer survivors remaining severely immunocompromised, with advanced age and comorbidities
4. Urgent need to improve medical skills of ICU specialists, develop remote patient management, and set up expert networks
5. Achieving a consensus on the standard of care to be offered for critically ill cancer patients in industrialized countries
6. Establishing universal criteria for the timing of ICU admission for cancer patients
7. Establishing, validating, and spreading standard procedures and protocols to optimize patient management and outcomes
8. Improving our understanding of organ dysfunction with the hope of improving organ recovery and increasing the proportion of patients fit for intensive curative treatments
9. Gathering multicenter data on outcomes associated with time-limited trials, with a special focus on the balance between avoiding both premature end-of-life decisions and giving nonbeneficial care
10. Introducing early palliative care for critically ill cancer patients

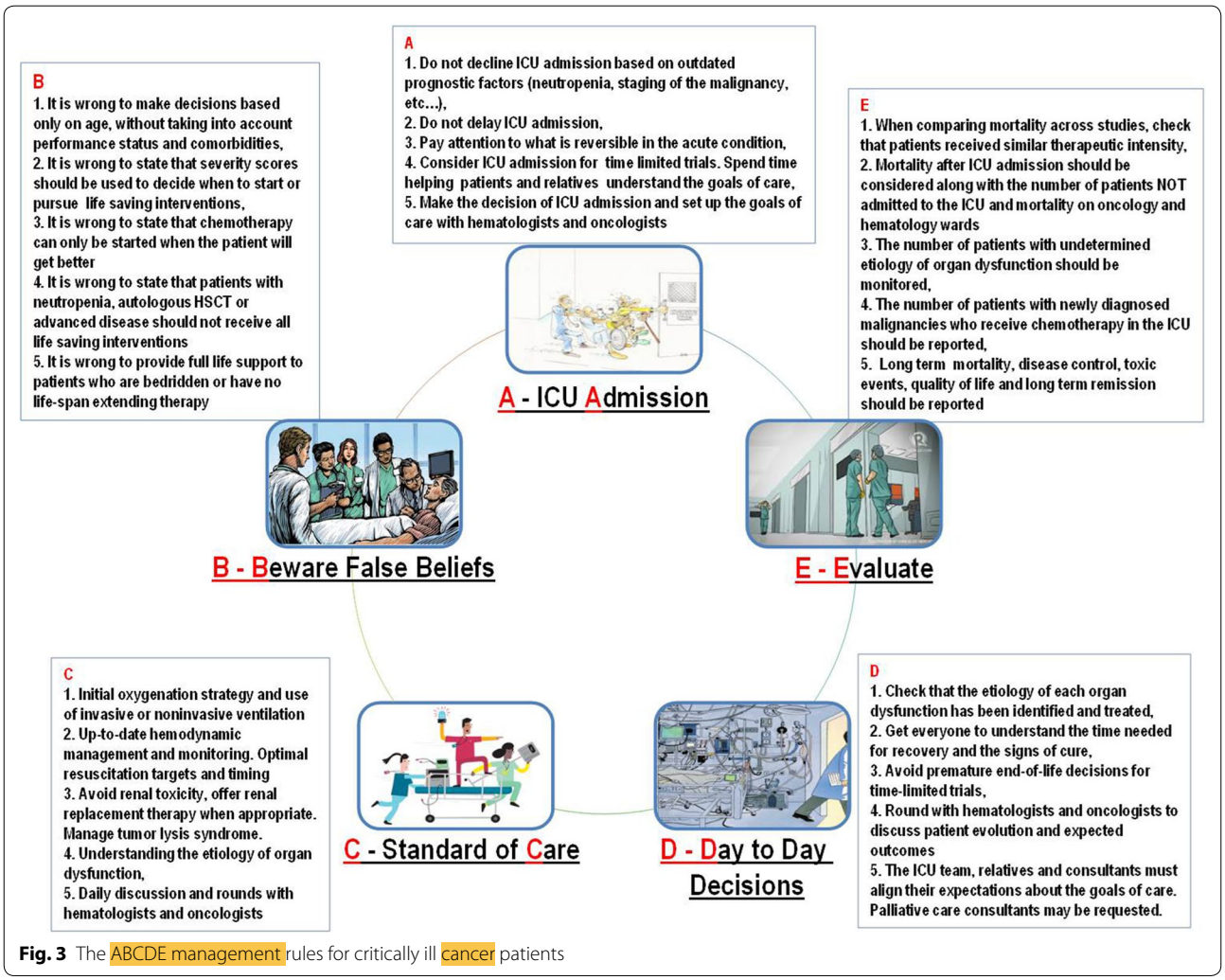

Fig. 3 The ABCDE management rules for critically ill cancer patients

by the broad range of potential pathogens and their varying antimicrobial susceptibility [100, 126]. These factors led to excessive prescription of antibiotics and antifungals, but also sometimes to undertreatment. Diagnostic strategies may incorporate newer tests with higher diagnostic performances, shorter turnaround time, and easy and noninvasive sampling. These may include classic or new approaches to the use of biomarkers reflecting host response or pathogen invasion and non-culture-based microbiological identification of pathogens [127, 128]. Biomarkers may allow better differentiation of infectious from noninfectious conditions, earlier detection of invasive pathogens, and safer withholding of antibiotic therapy [129, 130]. Molecular techniques such as those based on nucleic acid extraction and amplification may identify pathogens and key resistance genes in less than 12 h and thus guide early antibiotic choices [128].

Research should now focus on interventional trials comparing diagnostic strategies with and without these tests incorporated. Beside mortality, additional outcomes should be economic and ecological costs, such as antimicrobial consumption and emergence of resistance. The cost–benefit ratio of newer diagnostic tests and especially the added value compared with state-of-the-art clinical decision-making [131] should be addressed. In addition to noninvasive samples, these tests also need to be tested in CT-guided fine needle biopsy or endobronchial ultrasound-guided biopsy. Lastly, the excellent negative predictive value of some biomarkers does allow exclusion of a diagnosis, avoiding undue treatment toxicity and extra costs [132].

Tailoring therapy to biomarkers

Of the vast array of inflammatory markers, procalcitonin has been most extensively investigated [130]. Specificity and sensitivity are too low to guide initiation of antibiotics in cancer patients with suspected sepsis, leaving this decision to be taken on clinical grounds [129, 133].

Procalcitonin might possibly be used to guide duration of antibiotic therapy in critically ill cancer patients with sepsis [129].

Regarding AKI, in addition to creatinine, tubular injury markers such as NGAL or cell cycle arrest markers (TIMP-2, IGFBP7) [134–136] have been evaluated to detect renal injury or stress. While these biomarkers might provide additional insight into the pathophysiology of AKI and have predictive value, they are currently not used in daily clinical practice [137]. Although several strategies to prevent further renal damage in patients with (or at risk of) AKI are available [138], determination of a biomarker does not have therapeutic consequences at the moment.

Studies are needed to describe the kinetics and predictive value of markers of both inflammation and renal injury in this specific group. Last, research should address the safety of antibiotic-sparing measures (de-escalation, shorter courses, biomarker-guided decision trees) in cancer patients with and without neutropenia and whether these are effective for limiting emergence of resistance.

Impact of critical illness on long-term outcomes

We suggest including variables such as disease-free and event-free survival, as well as quality-adjusted life-years (QALYs) in studies on critically ill cancer patients. Also, assessment, treatment, and prevention of post intensive care syndrome in this population is important. Moreover, acute brain dysfunction is highly prevalent in mechanically ventilated patients with cancer [139], and long-term cognitive impairments occur in patients that develop delirium in the ICU [140]. An increased number of patients are discharged alive from hospital. However, advances in community palliative care and the increasing number of hospices have made it possible for patients to be discharged from hospital to die at home or in a hospice. Studies to better identify a patient's trajectory following ICU discharge are warranted. Similarly, additional studies are warranted to show that critical care management serves as a bridge to optimal therapy and cure. Such data will encourage clinicians to use alternative strategies of ICU admission (mostly time-limited trials). Studies to demonstrate that earlier recognition of cancer patients at risk of life-threatening deterioration and potential benefits from rapid response teams are needed. Moreover, more data are needed to guide clinicians on a daily basis during time-limited trials. Finally, in cancer patients, who at best are discharged to the wards to receive curative treatment, studies are warranted to assess the impact of early rehabilitation and transition programs on ICU-acquired weakness, functional status, sarcopenia, and other physical outcomes that are affected by both critical illness and the malignancy.

Understanding/managing toxicity of targeted therapy, immunotherapy, and biotherapy

Optimal dosing of targeted therapy and biotherapy is not well established and they have a narrow therapeutic margin. Pulmonary toxicity is rare but life-threatening and includes bronchospasm, pneumonitis, acute respiratory distress syndrome, diffuse alveolar hemorrhage, pleural effusion, and pulmonary hypertension [141, 142]. The diagnosis remains one of exclusion, and rechallenge should be discouraged. Early cessation of the drug is the best treatment. Corticosteroids may be useful. Monoclonal antibodies provoke a wide variety of systemic and cutaneous adverse events, including the full range of true pulmonary, cardiac, liver, or renal hypersensitivities, which can be fatal. We encourage the critical care community to open a registry of critically ill cancer patients admitted to the ICU for treatment of the side effects of targeted therapy and biotherapy. Also, improving intensivists' skills to recognize and diagnose these side effects could be one of the secondary outcomes of interventions enhancing dialogue between oncologists/hematologists and intensivists on a daily basis. Lastly, as tumor lysis syndrome will be increasingly encountered in patients with solid tumors receiving immunotherapy, clinicians need to be aware and prepared.

Transfusion policies

As mentioned above, it would be desirable to establish the indications for early RBC transfusion as part of initial resuscitation from severe sepsis in cancer patients, in whom hemoglobin is frequently chronically reduced. Also, besides mortality, the optimal transfusion threshold in the case of persistent tissue dysoxia and altered lactate clearance has to be established [60, 61]. Last, studies to clarify indications and thresholds for platelet transfusions in cancer patients with thrombocytopenia are warranted.

Moving back from noninvasive to invasive management

At the end of the 1990s, noninvasive diagnostic and therapeutic management were believed to be the best ways to avoid worsening the patient's status and increasing mortality [32]. Indeed, mortality of patients intubated was as high as 90%, making NIV a life-saving intervention [32]. Also, severe hypoxemia, thrombocytopenia, and hemostatic disorders have discouraged invasive diagnostic strategies such as BAL and lung, liver, or kidney biopsies, placing biomarkers and molecular biology techniques at the forefront of noninvasive diagnostic tests. However, the mortality associated with intubation has decreased

substantially amid increasing evidence that hypoxemic patients with tachypnea have a high respiratory drive and may inflict ventilator-induced lung injury on their lungs [41]. Moreover, the use of NIV or HFNC has made FOB-BAL safer, and CT-guided minimally invasive biopsies have a high diagnostic yield with a relatively low frequency of side effects [143]. We recommend again evaluation of invasive versus noninvasive diagnostic and therapeutic strategies. Also, noninvasive diagnostic tests should be compared to minimally invasive biopsies. Studies are needed to better document whether delayed intubation related to trial of NIV, CPAP using a facial device or a helmet, or HFNC actually increases mortality. Here, careful continuous and precise monitoring of expiratory tidal volumes under NIV should be performed and its relation to mortality reassessed.

Rescue strategies for cancer patients with ARDS

Corticosteroids have been tested in patients with leukemic infiltrates, *Pneumocystis* pneumonia, diffuse alveolar hemorrhage, or acute interstitial pneumonia without documented infection, but the level of evidence remains weak [144]. The improvement in oxygenation should be balanced against the increased rate of secondary infections, specifically invasive fungal infections and viral reactivation.

The 90-day mortality of cancer patients with severe ARDS remains above 80% [42]. No study is currently available on the benefits of recruitment maneuvers, nitric oxide, and prone positioning in cancer patients. Moreover, it is obvious that cancer patients are deprived of several rescue strategies. ECMO to avoid mechanical ventilation or as a rescue strategy in hematologic patients and after allogeneic SCT has been reported, with poor results and remarkably high complication rates [46, 111, 145] We propose outcome studies on cancer patients with severe ARDS potentially eligible for ECMO by accepted criteria [146]. The use of non-ECMO rescue strategies and of ECMO would be compared to theoretical indications, and the attributable survival of the technique could be estimated. Depending on the results of these studies as well as findings in non-cancer populations, a well-designed prospective ECMO trial might be considered in patients with malignancies.

Stem cell transplantation in the ICU

Recipients of hematopoietic stem cell transplantation (HSCT) still have a very low survival rate when they become critically ill and require life-sustaining therapies [147]. Although it is usually considered a safe procedure, autologous HSCT still carries a potential for life-threatening complications during the engraftment period, mostly related to the toxicity of high-dose chemotherapy and infections. However, extensive life support while waiting for recovery from neutropenia allows the survival of the large majority of patients. In allogeneic HSCT, however, life-threatening complications are not restricted to the acute toxicity of the conditioning regimen and to infections during the engraftment period, but also extend beyond day 30 because of sustained immunodeficiency as well as specific immune-related complications, both being mainly driven by graft-versus-host disease (GVHD) [148, 149]. It is classically recommended that ICU admission with maximal life support should be offered to patients within the engraftment period, whereas it is more questionable in patients with GVHD [121]. Studies to demonstrate that GVHD is no longer a binary variable (present or absent) but should be better defined by the response to therapy (controlled or stabilized with steroids, uncontrolled, refractory) are warranted. We suggest gathering more data on the trajectory of GVHD in ICU patients and its relation to survival.

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Compliance with ethical standards

Conflicts of interest

Elie Azoulay is part of the board of Gilead Sciences. He has received fees for lectures from Gilead, Astellas, Alexion, and Baxter. His institution has received support from Alexion, Gilead, Fisher & Payckle, Jazz Pharma, Pfizer and Cubist. Other authors declare no conflict of interest in relation with this manuscript.

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