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REVIEW

Managing critically Ill hematology patients: Time to think differently

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ABSTRACT

The number of patients living with hematological malignancies (HMs) has increased steadily over time. This is the result of intensive and effective treatments that also increase the probability of infiltrative, infectious or toxic life threatening event. Over the last two decades, the number of patients with HMs admitted to the ICU increased and their mortality has dropped sharply. ICU patients with HMs require an extensive diagnostic workup and the optimal use of ICU treatments to identify the reason for ICU admission and the nature of the complication that explains organ dysfunctions. Mortality of ARDS or septic shock is up to 50%, respectively. In this review, the authors share their experience with managing critically ill patients with HMs. They discuss the main aspects of the diagnostic and therapeutic management of critically ill patients with HMs and argue that outcomes have improved over time and that many classic determinants of mortality have become irrelevant.

1. Background

In most industrialized countries, the number of patients living with hematological malignancies (HMs) has increased steadily over the last two decades, for several reasons [1]. The diagnosis is made earlier, when treatments are more effective, and molecular biology advances help to recognize low-grade malignancies consistent with normal life for many years [2]. Effective high-dose treatment regimens and targeted treatments have been introduced. These changes have considerably increased survival with good quality of life [3–5].

Patients with HMs increasingly require admission to the intensive care unit (ICU) for life-threatening events related to the malignancy and/or treatments, with immunosuppression being a major contributor [6,7]. Also, the aging of the population and development of specific treatment strategies for elderly patients [5,8,9] have increased the proportion of ICU admissions for comorbidity decompensation to about 20% among patients with HMs [10].

ICU patients with HMs require an extensive diagnostic workup [11] and the optimal use of available treatments [12]. Only close collaboration among hematologists, intensivists, and other specialists can meet these requirements [12]. The diagnosis and treatment of acute respiratory failure has been the most controversial issue over the past two decades [13–15]. Research fueled by this controversy has resulted in a sharp drop in mortality, from nearly 100% to about 40% [16]. Lung biopsies are now rarely needed, and bronchoscopy with bronchoalveolar lavage (BAL) is deemed useful only in selected patients [11]. In patients receiving mechanical ventilation (MV), mortality ranges from 35% to 70% depending on the associated organ dysfunctions and presence of graft versus host disease (GVHD) [17]. Mortality in patients with HMs and septic shock has fallen by 30% [18,19]. Non-bone marrow transplant (BMT) recipients with HMs requiring renal replacement therapy (RRT) have the same long-term outcomes as do patients without malignancies [20,21]. However, these data come from high-volume centers [22]. Moreover, they are probably influenced by selection bias, as up to 50% of patients referred for ICU admission are not admitted [10,23]. Although the current literature strongly suggests improved survival of

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ICU patients with HMs, data showing better short and long term outcomes with increased use of critical care services are lacking [16,19,24–26].

Here, we share our experience with managing critically ill patients with HMs. We chose to focus on the most recent studies, which were usually done in high-volume centers. The outcomes reported in these studies may not apply to every hospital. However, they can probably be achieved in many centers by clinicians strongly committed to providing optimal care to patients with HMs. We discuss the main aspects of the diagnostic and therapeutic management of critically ill patients with HMs. Our review, although not exhaustive, provides sound evidence that outcomes have improved over time and that many classic determinants of mortality have become irrelevant (Table 1). Thus, the data in this review is of a nature to substantially affect clinical practice.

2. Changes in admission policies: more ICU admissions, increased survival

In recent decades, mortality has dropped sharply among patients with HMs admitted to the ICU [18,27], including those requiring MV (Figs. 1 and 2). Consequently, the number of such patients admitted to the ICU has increased [6,7]. Importantly, patients admitted in recent years are sicker [6]: thus, lesser disease severity does not explain the survival gains. Whether the increase in ICU admissions is related to increased referrals by hematologists and/or to increased admissions by intensivists is unknown. The criteria used for ICU referral and admission decisions have not been extensively evaluated. Finally, the links between admission policies and treatment-limitation decisions are unclear, but ICUs with broad admission policies may change the treatment goals based on the response to several days of full-code management.

Patients with HMs are still widely believed to have dismal outcomes should they become critically ill [23]. In a prospective study, we found that about half the patients with cancer referred for ICU admission were not admitted, because they were deemed either too well or too sick to benefit [28]. Mortality was 21% and 74% in these two subgroups, respectively. Thus, the clinical evaluation was neither sensitive nor specific for selecting patients for ICU admission, indicating a need for new admission policies [28].

3. Close and forthright collaboration with hematologists is mandatory

Several studies demonstrated a case–volume relationship in critically ill patients with malignancies [22]. In our experience, high-quality communication between hematologists and intensivists improves patient management in several ways [6,29]. The patients have two simultaneous needs: immediate supportive treatment for organ dysfunctions, which is available only in ICUs; [28] and control of the HM and its complications including drug-related toxicities. Hematologists may be more likely than intensivists to be aware of recent advances in HM diagnosis, treatment-related organ toxicities, or susceptibility to infections. Having both the hematologist and the intensivist provide information to the patients and families is likely to paint a clearer picture of realistic outcomes. Collaboration between hematologists and intensivists is invaluable to resolve the more complex problems and to determine when shifting from curative to palliative care is appropriate. In practice, when hematology patients are in the ICU, hematologists need to be contacted as early as possible to share discussions about the goals of care, to help identify the reason for ICU admission (they may be at the forefront for newly diagnosed malignancies, diagnoses such as drug-related toxicity, relapse, or disease-related complication), and communicate with the relatives. On a daily basis, hematologists and intensivists follow patient's evolution and make together decisions each in the field of expertise.

When patients with HMs are admitted to the ICU, they should experience no decrease whatsoever in the level of hematological expertise available to them. Instead, the expertise of the ICU team adds to that of the hematologists in an effort to provide the life-supporting interventions required by their acute illness [12].

Table 1
Variables no longer associated with hospital mortality after ICU admission.

1. Neutropenia
2. Autologous bone marrow transplantation[a]
3. Physiological severity scores
4. Type of hematological malignancy
5. The complicated issue of age (ability to tolerate chemotherapy, burden of age-related comorbidities)
6. Stage of the disease (because patients are selected by hematologists on these criteria)
7. Second-line therapies
8. Blood transfusion requirements
9. Multidrug-resistant bacteria/emerging highly resistant bacteria
10. Multiorgan failure in patients with macrophage activation syndrome or tumor lysis syndrome.

[a] Allogeneic bone marrow transplantation remains associated with hospital mortality after ICU admission. SOFA, Sequential Organ Failure Assessment.

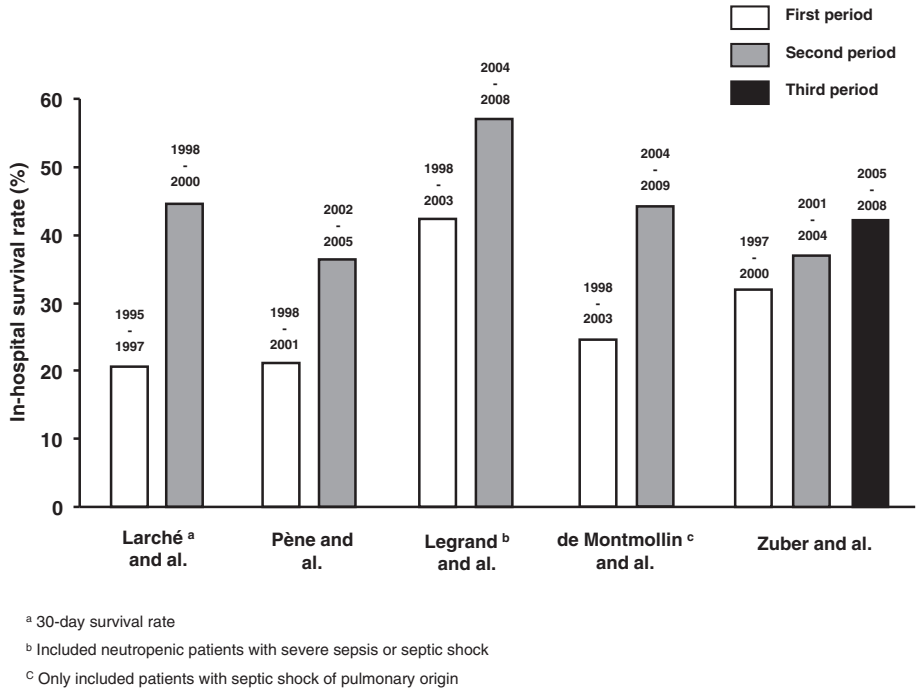
4. Delayed admission to the ICU is associated with lower survival (Fig. 3)

The finding that patients with multiple organ dysfunction and high organ failure scores at ICU admission have higher mortality rates has generated several hypotheses regarding the possible link between delayed ICU admission and mortality [13]. High acute-illness severity at ICU admission can be ascribed to five factors. First, patients may interpret acute symptoms as inevitable manifestations of their malignancy or may lack the social support or financial resources needed to obtain medical advice [16]. Second, ICU referral or admission decisions may be extraordinarily difficult when the prognosis is unclear [10]. Third, a delay in optimal care may arise from the initial admission to an ICU ill-equipped to manage patients with HMs [30–32]. Fourth, suboptimal evaluation on the wards may result in underestimation of disease severity followed by an unexpected clinical deterioration [32,33]. Lastly, acute illnesses can run a fulminant course in patients with severe immunodeficiency (e.g., neutropenia and other qualitative or quantitative immune-cell alterations) [32], so that the organ dysfunctions are maximally severe despite prompt ICU admission.

The first four reasons listed above are amenable to improvement. Useful measures may include patient education, education of physicians involved in ICU referral or admission and in evaluating and monitoring patients with HMs, education of intensivists about the management of patients with HMs, and greater availability to less experienced intensivists of advice from intensivists at centers managing large numbers of patients with HMs.

5. Reasons for decreased mortality in critically ill patients with hematological malignancies

The marked drop over recent years in short-term mortality after ICU admission of patients with malignancies (Figs. 1 and 2), despite an increase in acute illness severity, has been documented in both unselected patients and in patients with sepsis or ARDS [27]. Possible confounding factors that have not been properly investigated deserve careful attention. First, changes in triage policies for ICU admission select those patients most likely to benefit from life-sustaining interventions. However, our deep conviction is that some nonadmitted patients may benefit from ICU admission, i.e., that current triage policies are suboptimal [23]. Second, in several studies 10% to 40% of critically ill patients with HMs had received hematopoietic stem-cell transplants (HSCTs) [35,36]. A higher proportion of allogeneic HSCT recipients results in lower survival [34,37]. Third, no accurate data are available on the ICU mortality decrease in the overall population of critically ill patients, although



[a] 30-day survival rate

[b] Included neutropenic patients with severe sepsis or septic shock

[C] Only included patients with septic shock of pulmonary origin

Fig. 1. Temporal trends in survival of septic shock in patients with cancer managed in GrrrOH-affiliated centers. GrrrOH designates *Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique*. Only the Zuber's was a multicenter study.

its magnitude seems far smaller compared to that in patients with HMs. Fourth, high-quality collaboration between intensivists and hematologists plays a major role in the correct deciphering of pathophysiological mechanisms [31,38,39] and optimal management of toxicities, thereby improving patient outcomes. Intensivists must receive specific training in hematology, and hematologists must be trained to recognize the early physiological derangements that herald shock, acute respiratory failure, or acute kidney injury. Similarly, decisions about ICU admission and the timing of ICU interventions must be discussed openly.

An essential point is flexibility in the decision-making process to reflect the steady improvements in outcomes [28], regular introduction of new treatments, and continual changes in concepts based on new data. Many classic predictors of mortality are no longer relevant [28]. For instance, Table 2 reports mortality in ICU patients with neutropenia showing same survival than in general critically ill hematology patients. Thus, the standard of care must be updated continuously based on the most recent advances.

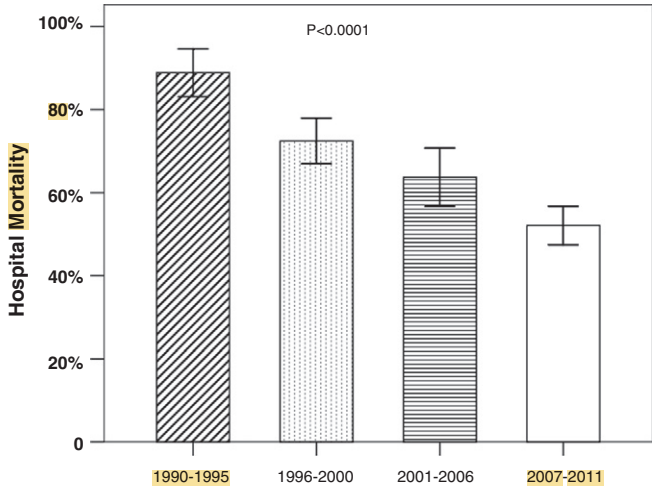


Fig. 2. Hospital mortality in 1004 patients with ARDS managed in GrrrOH-affiliated centers according to period of intensive care unit admission. Figure from Azoulay et al. [27] published in Intensive Care Medicine and copied here with permission. GrrrOH designates *Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique*.

6. The long-term: are we prolonging life or extending the dying process? The ICU as a bridge to cure

This section could not have been written 5 years ago, as it rests on very recent data. Four recently published studies provide sound information

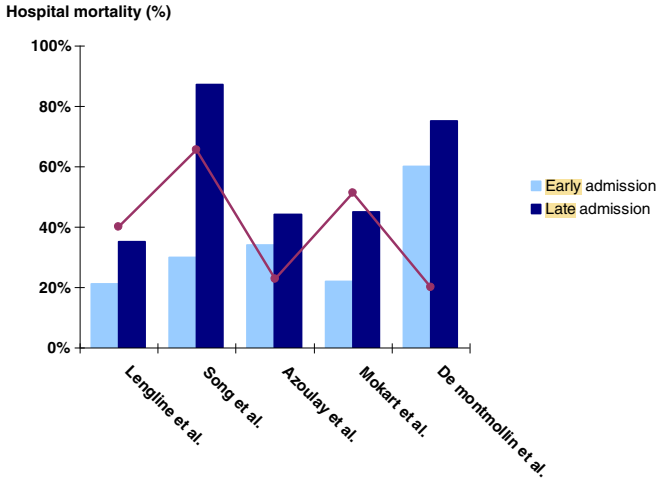


Fig. 3. Hospital mortality in patients with delayed ICU admission. Lengliné et al. compared patients with acute myeloid leukemia admitted to the ICU with or without organ dysfunction and found a difference of 1 day in time to ICU admission. Song et al. compared mortality in 199 patients admitted to the ICU 0.5 h vs. 4.7 h after the onset of shock. Azoulay et al. compared time from hospital to ICU admission in 1011 unselected patients with hematological malignancies. Mokart et al. and De Montmolin et al. compared time from hospital to ICU admission in patients with acute respiratory failure or septic shock from pneumonia, respectively. The light blue bars indicate mortality after early ICU admission and the dark blue bars mortality after delayed ICU admission. The red line represents the relative reduction in mortality between groups in each study.

Table 2
Outcomes in critically ill patients with neutropenia.

Year	Author	Design	Setting	Critical illnesses	Type of patients	Key messages
2015	Mokart	Observational prospective	ICU	Neutropenia	289 hematology patients	Hospital mortality was 45.3%. Allogeneic HSCT/BMT, need for mechanical ventilation, microbiological documentation, and need for renal replacement therapy, age and neutropenic enterocolitis were associated with mortality.
2014	Mokart	Observational prospective	ICU	Severe sepsis, septic shock	101 NP	Antibiotic de-escalation (44% of cases) is not associated with short- or long-term mortality.
2014	Mokart	Observational prospective	ICU	Severe sepsis, septic shock	118 NP	ICU mortality is associated with a time to antibiotic treatment >1 h
2014	Rosa	Observational prospective	Ward	FN and septic shock	307 NP	FN with polymicrobial bacteremia or BSI by *Streptococcus viridans* or *Escherichia coli* are at increased risk of septic shock.
2013	Mokart	Observational retrospective	ICU	ARF	123 NP	IMV is associated with hospital mortality, whereas neutropenia recovery and corticosteroid treatment are associated with hospital survival.
2012	Legrand	Observational retrospective over 10 years	ICU	Severe sepsis, septic shock	428 NP	Hospital survival has improved over time. Early catheter removal in undocumented sepsis and use of aminoglycosides improve survival. Acute non-infectious situations are associated with mortality.
2012	Mokart	Observational prospective	ICU	ARDS	72 NP	28-day survival is associated with lobar ARDS, initial antibiotic therapy active on DTT bacteria, and first-line chemotherapy.
2011	Povoa	Observational	ICU	Sepsis	86 NP vs. 68 NNP	Among critically ill cancer patients, those with neutropenia have higher CRP concentrations.
2011	Souza-Dantas	Matched-case control study	ICU	Any critical illness	94 NP vs. 94 NNP	Neither neutropenia nor recent chemotherapy is associated with ICU or hospital mortality.
2010	Alves	Observational prospective	Ward	FN and septic shock	41 NP	During FN, Ang-2 and Ang-2/Ang-1 ratio predict septic shock.
2010	Hamalainen	Observational prospective	Ward	FN and severe sepsis	70 NP	Neither serial NT-proBNP nor CRP predicts severe sepsis.
2010	Jeddi	Observational prospective?	Ward	FN, severe sepsis	41 NP	Hypophosphatemia, hypoproteinemia, and initial non-adapted antibiotic therapy predict severe sepsis.
2010	Mato	Case–control study	Ward	FN, septic shock	547 NP	During FN, lactate concentration (≥2.5 mmol/L) and tachypnea predict septic shock.
2009	Rhee	Observational retrospective	ICU	ARDS, neutropenia recovery	71 NP	Pneumonia during neutropenia is a risk factor for ARDS around neutropenia recovery.
2008	Mokart	Observational prospective	ICU	ARDS	12 NP vs. 10 NNP	Circulating monocytes are deactivated during neutropenic ARDS.
2007	Ramzi	Observational prospective	Ward	FN and septic shock	20 NP, 110 episodes of FN	Pulmonary infection and lactates >3 mmol/L predict septic shock.
2006	Gomez	Observational	Ward	FN	167 NP, 238 episodes of FN	Systolic hypotension, high respiratory rate, comorbidities, and a clinical site of infection predict serious complications.
2005	Karlin	Observational retrospective	ICU	ARF during neutropenia recovery	20 NP	Time from respiratory symptoms to neutropenia recovery was 1 day; 5 patients died from ARDS.
2003	Mokart	Observational prospective		Septic ARDS	17 NP vs. 23 NNP	BAL in neutropenic ARDS patients show alveolar macrophage deactivation, possibly linked to the use of G-CSF.
2003	Regazzoni	Observational prospective	Ward ICU	FN, SIRS, septic shock	62 NP	Mortality and progression to septic shock are associated with the number of SIRS criteria at admission.
2002	Azoulay	Observational retrospective	ICU	ARDS, neutropenia recovery	62 NP	ARF patients with prolonged neutropenia and pneumonia are at increased risk of ARDS.
2002	Darmon	Observational retrospective	ICU	Neutropenia recovery, any critical illness	102 NP	30-day mortality is associated with ARF or AKI; survival is associated with neutropenia recovery.
2000	Staudinger	Observational retrospective	ICU	Any critical illness	157 of 414 cancer patients	Mortality associated with respiratory insufficiency, need of mechanical ventilation, and development of septic shock. ICU mortality was 100% when APACHE III score was of >80
2000	Gruson	Retrospective case-series analysis	ICU	Any critical illness	28 NP treated with G-CSF vs. 33 NP without G-CSF	G-CSF use is not associated with ICU outcome.
2000	Gruson	Observational prospective	ICU	Pulmonary infiltrates	93 BAL in 93 NP	BAL has a low complication rate, infrequently leads to treatment modifications, and is not associated with improved survival when a diagnostic is established.
2000	Hilbert	Observational prospective	ICU	ARF	64 NP with ARF treated with CPAP	CPAP is efficient in 25% of cases, and all responders survived.
1999	Bouchama	Case–control study	ICU	Any critical illness	30 NP treated with H-CSF vs. 30 NP without H-CSF	H-CSF does not improve ICU survival or neutropenia recovery.
1998	Ewig	Historical cohort study	Ward	1st episode of pulmonary infiltrates	53 NP	HR/SBP ratio ≥1.2, radiographic score ≥3, and persistent neutropenia are associated with death.
1998	Guiguet	Observational prospective	ICU	Any critical illness	94 NP	SAPS II and the number of acute organ failures at ICU admission predict outcome. The course of acute organ failures during the first 3 days following ICU admission is associated with the outcome.
1997	Blot	Observational retrospective	ICU	Any critical illness	107 NP	The number of organ failures and ARF within the first 24 h after ICU admission is associated with ICU mortality.
1985	Ognibene	Observational retrospective	ICU	ARDS, histological analysis	11 NP	ARDS can occur during severe neutropenia without neutrophil infiltration.

ICU, intensive care unit; NP, neutropenic patients; NNP, nonneutropenic patients FN, febrile neutropenia; BSI, bloodstream infection; ARF, acute respiratory failure; IMV, invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; DTT, difficult to treat; CRP, C-reactive protein; Ang, angiopoietin; NT-proBNP, N-terminal pro-brain natriuretic peptide; BAL, bronchoalveolar lavage; AKI, acute kidney injury; G-CSF, granulocyte colony-stimulating factor; SIRS, systemic inflammatory response syndrome; CPAP, continuous positive airway pressure; H-CSF, hematopoietic colony-stimulating factor; HR, heart rate; SBP, systolic blood pressure; SAPSII, Simplified Acute Physiology Score.

on outcomes of patients with HMs who survive an ICU stay. Additional studies from different centers are needed to confirm this information. The first study included only patients with acute myeloid leukemia managed in a single center in Vienna and found short-term outcomes consistent with recent findings [40]. Thus, patients requiring ICU admission had lower survival rates compared to other patients. Interestingly, 30 days after ICU admission, ICU survivors had similar survival rates and complete remission rates than did the nonadmitted patients. These data were confirmed by another study, from Canada [41]. We prospectively studied 1011 patients with HMs managed in 17 ICUs in France and Belgium [10]. Importantly, 80% of ICU survivors were in complete remission after 6 months, with a health-related quality of life similar to that in cancer patients with no history of ICU admission [10]. Another study, from Belgium, also assessed quality of life in ICU survivors with HMs [42].

These studies of long-term outcomes in patients with HMs assessed several months after ICU discharge constitute external validation of current practices and identify ICU admission as a bridge to a cure or to long-term control of the malignancy. Thus, appropriate ICU does not extend the dying process but, instead, prolongs life and can increase disease-free survival. Nevertheless, we believe that palliative ICU management can be offered to highly selected patients with HMs [43], although this approach is only very rarely warranted. In a multicenter observational study of patients receiving noninvasive ventilation for acute respiratory failure, up to 18% of the patients had treatment-limitation decisions, including chiefly cancer patients [43]. Of striking finding, survival was 56% in patients with who declined tracheal intubation (do-not-intubate – DNI – patients). Day-90 survivors exhibited similar quality of life compared to before ICU admission. Furthermore, patients and relatives of DNI patients exerted no significantly different quality of life compared to patients with no treatment-limitation decisions. This study has provided important perspectives with possibly far-reaching clinical implications. Importantly, in this situation, the goals of care must be communicated clearly to the patients, relatives, and healthcare providers. Intermediate-care and step-down units may provide optimal conditions for shifting from curative to comfort care should an ICU trial fail. Our personal experience and data from the literature have convinced us that the ICU does not provide the best likelihood of experiencing a good death [44–46].

7. Can we recognize patient subgroups unlikely to benefit from ICU management?

Readers, please, do not construe this paragraph as an invitation to routinely deny ICU admission to patients meeting certain criteria. Medical decisions cannot be entirely objective, if only because none of the available outcome prediction tools works perfectly, and must be taken for each individual patient. Nevertheless, some clinical situations are associated with nearly 100% mortality despite optimal care. Should an ICU trial be performed in these situations, the expected outcomes must be clearly communicated to the patients and relatives. In this section, we will not consider the increasing subgroup of patients who decline ICU admission based on either a previous difficult ICU experience or personal preferences and values.

Over the last three decades, several research groups have reported consistent data identifying ten patient subgroups unlikely to derive survival gains from ICU management (Table 3). For each subgroup, we will discuss remaining issues and suggest directions for future investigation.

Table 3
Ten patient subgroups unlikely to benefit from ICU management.

- •Bedridden patients
- •Patients with no lifespan-extending treatment options for their hematological malignancy
- •Elderly patients with significant comorbidities
- •Patients with multiple or severe comorbid conditions (COPD, heart failure, cirrhosis of the liver)
- •Patients with less than 6 months of life expectancy
- •Allogeneic BMT/HSCT recipients with steroids-uncontrolled GVHD
- •Patients with invasive pulmonary aspergillosis requiring endotracheal mechanical ventilation
- •Patients with persistent multiple organ failure
- •Patients with newly diagnosed malignancies unresponsive to chemotherapy started in the ICU
- •Patients experiencing a recurrent life-threatening event after ICU discharge, with prolonged and complex interventions during the first ICU stay and several residual organ dysfunctions at discharge (e.g., dialysis, oxygen, neurologic dysfunction, liver failure, heart failure)

ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; BMT, bone marrow transplant; HSCT, hematopoietic stem cell transplant; GVHD, graft-versus-host disease.

7.1. *Bedridden* patients

Performance status, when assessed, was consistently an independent risk factor for short-term mortality in both patients with HMs and the overall ICU population [10,47]. This factor is both readily assessed and extremely reliable. Highly dependent or bedridden patients are usually not referred or admitted to the ICU [23,47]. A poor performance status usually reflects irreversible factors such as very old age or severe comorbidities [48], which can be assessed using the Charlson comorbidity index [10]. However, the malignancy itself can explain a poor performance status if it involves the heart (e.g., amyloidosis), respiratory system (e.g., pleural involvement or interstitial lung disease), or bone and neurological system (e.g., myeloma and lymphoma). Malignant infiltration of the gastrointestinal tract or kidneys can lead to massive protein losses with intractable malnutrition, whose correlate is increased vulnerability to severe infections and toxicities induced by drugs, particularly chemotherapeutic agents. Lastly, patients with lymphoma-related hemophagocytic lymphohistiocytosis may have newly diagnosed lymphoma and a major alteration in general health with multiple organ dysfunctions that preclude the administration of optimal chemotherapy [39]. No study has demonstrated that the reason for the general health decline is associated with specific outcomes. Investigations are needed to assess how performance status impacts short-term survival and to determine whether a subgroup of dependent or bedridden patients may regain self-sufficiency after optimal hematological and intensive care.

7.2. *Patients with no lifespan-extending treatment options*

These patients usually fail to benefit from ICU management [16]. The goal of ICU admission of patients with HMs is to extend long-term survival and can be achieved only if the malignancy is under control. Three important clarifications are in order. First, patients do not have to be in remission to be admitted to the ICU. ICU admission may very well be appropriate for patients who have newly diagnosed high-risk malignancies requiring organ support simultaneously with chemotherapy initiation, life-threatening sepsis with or without neutropenia, or treatment toxicities. Most of the patients are not yet at the stage where their remission status can be assessed. ICU management can also benefit patients with chronic HMs (e.g., myeloma, chronic lymphocytic leukemia, or low-grade lymphoma) that are still active [6,29]. Second, patients with HMs can achieve survival benefits from second-line chemotherapy: thus, failure of first-line chemotherapy does not necessarily argue against ICU admission. Cytogenetic data, high-dose therapy, and allogeneic HSCT/BMT should also be taken into account. Third, an increasing number of patients with refractory leukemia receive rescue HSCT/BMT in an attempt to achieve long-term disease control. Intensivists must make every effort to help patients and hematologists achieve the full benefits of the latest treatments for HMs. However, admission of excessive numbers of patients with uncontrolled disease and experimental treatment programs might adversely affect the commitment of ICU

Table 4
Outcomes in recipients of bone marrow/stem cell transplantation.

Study, year, journal	Design	Study period	N patients/N allogeneic/% all BMT/mortality (%)	MV (%/mortality)	Dialysis (%/%mortality)	Prognostic factors
Scott 2002 Anaesth Intens Care	Retrospective	1988–1998	92/–/–/–	50%/88%	/	
Kew 2006 BBMT	Retrospective	1992–2001	37/33/9%/63%	68%/–	/	Vasopressor use
Scales 2008 Critical Care	Retrospective	1992–2002	504/264/20%/67%	51%/87%	7%/94%	MV, dialysis
Kress 1999 AJRCCM	Retrospective	1993–1996	44/7/–/39%	45%/55%	/	MV, allogeneic BMT (all died)
Gruson 1999 Eur Respiratory journal	Retrospective	1993–1997	38/24/–/76%	84%/91%	/	Noninfectious respiratory failure, multiple organ failure
Price 1998 AJRCCM	Prospective	1994–1996	115/72/–/54%	42%/81%	16%/78%	MV, allogeneic BMT (80% died)
Bach 2001 Blood	Prospective, 5 centers	1994–1997	/	–/86%	/	Acute renal failure, hepatic dysfunction
Letourneau 2002 Nephron	Retrospective	1994–1998	57/42/13%/75%	/	25%/88%	Acute renal failure
Yang 2007 J Formos Med assoc	Retrospective	1994–2005	41/35/–/80%	/	–/100%	Age, APACHE2, vasoactive drugs)
Afessa 2003 CCM	Retrospective	1996–2000	112/50/–/51% (78% if allogeneic)	55%/74%	/	MV, APACHE3
Townsen 2013 Br J Haematol	Retrospective	1996–2007	164/164/–/68%	50%/86%	32%/86%	MV, conditioning intensity
Pène 2006 JCO	Retrospective, 3 centers	1997–2003	209/209/–/79%	58%/89%		Time From BMT, AGVHD, MV
Soubani 2004 Chest	Retrospective	1998–2001	85/45/–/39%	60%/63%	13%/73%	MV, multiple organ failure
Benz 2014 BMT	Retrospective	1998–2007	33/33/13%/64%	63%/94%	27%/–	Multiple organ failure
Agarwal 2012 Internal medicine Journal	Retrospective	1998–2008	123/107/–/62%	77%/–	32%/–	Multiple organ failure, fungal infection, CMV reactivation
Sohl 2012 BBMT	Retrospective	1998–2009	/	–/83%	/	Renal failure, platelet count
Kim 2003 Transplantation	Retrospective	1999–2001	18/–/9%/94%	94%/100%	94%/100%	APACHE2
Depuydt 2011 BMT	Retrospective	2000–2007	44/44/–/61%	73%/84%	27%/82%	Time from BMT, MV
Huyhn 2009 J Transplantation	Retrospective	2001–2006	154/94/25%/53%	71%/–	41%/–	Allogeneic BMT (62% died), MV, vasopressors
Bayraktar 2013 JCO	Retrospective	2001–2010	389/389/13%/64%	/	/	HCT-CI score, conditioning intensity, AGVHD
Gilbert 2013 BBMT	Retrospective	2006–2010	/	–/63%	–/90%	MV, liver dysfunction
Azoulay 2013 JCO	Prospective, 17 centers	2010–2011	145/145/–/52%	47%/71%	21%/77%	Allogeneic BMT

MV, mechanical ventilation; BMT, bone marrow transplantation; AGVHD, acute graft versus host disease, HCT-CI, hematopoietic cell transplantation-comorbidity index.

teams, who may feel that, given the finite nature of ICU resources, other patients more likely to survive are being deprived of optimal care.

7.3. *Elderly patients*

The issue of elderly patients is both important and complex. The aging of the general population is increasing the number of elderly patients with HMs. Also, except for Hodgkin lymphoma, the median age at diagnosis is older than 60 years for most HMs [1]. Furthermore, in hyperleukocytic acute myeloid leukemia, cytoreduction therapy with hydroxyurea can allow induction chemotherapy to be postponed by reducing early mortality. Subsequently, full-code ICU management can be provided based on cytogenetic and molecular biology results. The available data are not sufficient to make clear recommendations. Instead, general principles can be applied to avoid denying ICU admission to fit elderly patients who are older than 65 years but have an excellent performance status and no comorbidities. Age *per se* is not a risk factor for mortality [48] and should not serve as the sole criterion for ICU-admission decisions, although short- and long-term mortality and treatment unresponsiveness are more common after 60 years of age. We suggest the following empirical strategy: (a) unrestricted ICU admission for elderly patients with a good performance status, no advanced comorbidities, and little or no cognitive dysfunction; (b) determination of the balance between the burden of ICU management and life expectancy, the goal being to restore self-sufficiency for a period that is meaningful based on life expectancy; c) an ICU trial when no easy decision can be made or when noninvasive diagnostic or therapeutic management is likely to provide benefits. Importantly, an ICU trial should not be viewed as a means of resolving disagreements within the ICU team or among hematologists and intensivists. Instead, effective communication must be restored via skilled leadership, with the only goal of providing patients with realistic and appropriate treatment objectives.

7.4. *Patients with multiple or severe comorbidities (chronic obstructive pulmonary disease, heart failure, cognitive dysfunction, dementia, cirrhosis of the liver) regardless of age*

This situation can be encountered at any age. Comorbidities may preclude the administration of optimal chemotherapy, thereby jeopardizing the chances of controlling the HM. Palliative care is appropriate when no lifespan-extending treatments are available in patients with cirrhosis of the liver; advanced liver, heart, or respiratory failure; or other irreversible conditions.

7.5. *Patients with less than 6 months of life expectancy*

These very frail patients should receive appropriate information about the goals of care and expected outcomes from healthcare interventions. Also, decisions should be guided by the patient's preferences, values, and advance directives, via a collaborative decision-making process in which the primary-care physician has a major role to play. Palliative noninvasive ventilation, either as a therapeutic option [43] or as a means of alleviating respiratory distress [49], has been reported to improve short-term survival and quality of life [43]. The use of palliative vasoactive drugs in cancer patients has also produced high short-term survival [50].

7.6. *Allogeneic HSCT/BMT recipients with steroid-uncontrolled acute GVHD*

Graft versus host disease (GVHD) makes a big contribution to transplant-related mortality and is our major threat for allogeneic HSCT/BMT patients. Steroid-controlled GVHD still carries poor outcomes compared to critically ill patients with no GVHD [34]. Outcomes of septic shock, acute respiratory failure, and other critical conditions are dismal in these patients, to the extent that the use of life-sustaining interventions raises ethical issues [16,34,51–53]. When GVHD is controlled, or

at least stable, an ICU trial should be considered. However, when GVHD cannot be controlled despite a second line immunosuppressive therapy, ICU management appears inappropriate. Table 4 reports mortality rates in HSCT/BMT recipients. Importantly, several studies pooled allogeneic and autologous BMT recipients, limiting the relevance of their conclusions about patient management.

7.7. Patients with invasive pulmonary aspergillosis requiring intubation and mechanical ventilation

This subgroup includes patients with long-term neutropenia (acute leukemia or allogeneic BMT/HSCT), aggressive treatment for chronic lymphocytic leukemia (fludarabin and rituximab), or several lines of treatment [54]. When these patients require endotracheal mechanical ventilation, their outcomes are extremely poor [54]. However, recent studies have obtained promising results with voriconazole therapy, warranting a reappraisal of outcomes. Studies are needed to better define patients at high risk for invasive fungal infections despite absence of the classical risk factors, as the immune deficiency associated with critical illness and aggressive care increases the risk of unexpected invasive aspergillosis. Furthermore, patients with ARDS seem at high risk for invasive aspergillosis, and studies are needed to assess whether a trial of early antifungal therapy is warranted.

7.8. Patients with persistent multiple organ failure

In a study of HSCT recipients requiring MV, survival was 42% in patients with 0–1 additional organ failures compared to 13% in those with two or more additional organ failures. That the risk of death increases with the number of organ failures has been firmly established [22,55–57]. In our experience, the number of organ failures after several days of full-code ICU management is a better criterion on which to base the goals of care than is the number at ICU admission [28,58]. Thus, although mortality is very high in patients with multiple organ failures, some of these patients may improve rapidly with appropriate care (e.g., those with macrophage activation syndrome or tumor lysis syndrome). Moreover, in both immunocompromised and immunocompetent patients with acute respiratory failure, sepsis, or life-threatening toxicities who are admitted to the ICU late and/or with highly severe acute disease, multiple organ failures are associated with high mortality, yet some of these patients survive after a long ICU stay. There is no evidence that a specific duration of life-sustaining treatment or time from ICU admission to treatment initiation (intubation, dialysis, vasopressors etc…) is associated with mortality [10,33].

7.9. Patients with newly diagnosed malignancies with uncontrolled disease despite receiving chemotherapy in the ICU

The challenge when initiating chemotherapy in the ICU is to identify those patients likely to respond to chemotherapy and to achieve long-term survival and perhaps a cure. ICU management provides carefully selected patients with a chance of substantial disease-free survival. However, patients who are likely to be unresponsive to chemotherapy (based on cytogenetic findings, comorbidities, or advanced age precluding optimal chemotherapy) and those with persistent organ dysfunction (e.g., dependency on RRT or MV, or cognitive dysfunction) are unlikely to benefit from ICU admission with concomitant chemotherapy initiation.

7.10. Patients who need ICU re-admission after prolonged initial ICU management followed by multiple residual organ dysfunctions (RRT, oxygen therapy, neurologic dysfunction, liver failure, heart failure)

In these patients with persistent multiple organ failure, the need for ICU re-admission is an indicator of frailty and dependence. The possibility of ICU re-admission should be discussed thoroughly before discharge after the first ICU stay. Should an ICU trial be decided, the goals of care should be defined beforehand and the patient's preferences and values discussed. Hematologists and intensivists should work together to assess potential benefits and harms from ICU re-admission. They should also discuss the situation with the patients and relatives to avoid prolonging the dying process and having it occur in the stressful ICU environment [44].

8. The ICU as a collaborative diagnostic, therapeutic, and safety platform

In the near future, the ICU will probably be increasingly used to maximize patient safety during invasive or semi-invasive procedures. In ICUs and intermediate-care units, multiple specialists can work together to perform a clinical assessment, evaluate the feasibility of various treatments (based on comorbidities; cardiac, renal, and respiratory function; the geriatric assessment; and nutritional status), and promptly diagnose the malignancy itself or its infiltrative, toxic, or infectious complications. Identifying the disease and/or its complications is mandatory to provide the patient with targeted care. As the diagnoses are elucidated, a comprehensive roadmap can be provided to the patient and family.

It is likely that potential benefits from ICU management in patients with newly diagnosed malignancies come from various sources. One source is the set of interventions provided, including close monitoring, prompt diagnosis in patients receiving life-sustaining treatments, bleeding control, noninvasive diagnostic and therapeutic strategies in patients with acute respiratory failure, the use of appropriate tests not readily available on the wards (echocardiography), early antibiotics,

Table 5
Important questions regarding the ICU management of critically ill patients with hematological malignancies.

1. Do we have incontrovertible proof that ICU admission provides long-term survival benefits to patients with HMs?
2. Is the mortality difference across centers ascribable to differences in practice, such as timing of ICU admission, presence of a hematologist in the hospital, and the annual case–volume?
3. Is the mortality difference across centers ascribable to variations in therapeutic intensity and, more specifically, to inappropriate decisions to delay, withhold, or withdraw treatments?
4. What factors lead to delayed ICU admission (e.g., healthcare access, acuteness and severity of the disease, initial admission to a ward vs. the emergency department, inappropriate supportive care on the wards)?
5. Is induction chemotherapy best initiated in the ICU or the hematology ward in patients with newly diagnosed malignancies at high risk (or with mild levels of) acute respiratory failure, acute kidney injury, or cardiac or neurological complications?
6. What selection criteria do hematologists use for ICU referral? How effective are admission triage criteria used by intensivists?
7. Can early ICU admission improve survival or disease control by preventing the development and/or progression of organ dysfunctions and optimizing the feasibility of full-dose chemotherapy?
8. What is the optimal place for invasive versus noninvasive interventions? What benefits does noninvasive ventilation provide now that mortality has dropped from 90% to 50% in patients receiving invasive mechanical ventilation? Does noninvasive ventilation delay optimal management or is the association of NIV failure with increased mortality ascribable only to patient- and disease-related factors?
9. What is the optimal duration of full-code management in patients admitted for an ICU trial?
10. What is the best ICU management strategy in patients belonging to subgroups unlikely to benefit but for whom ICU admission has been decided based on a careful individual evaluation (e.g., allogeneic bone marrow transplant recipients with uncontrolled graft-versus-host disease or invasive pulmonary aspergillosis requiring mechanical ventilation)? Should the strategy be different from that used in other patient subgroups, e.g., more aggressive initially or, on the contrary, less invasive?

and timely chemotherapy. Another source is the set of interventions that are not provided, such as contrast agent use in patients at risk for acute kidney injury, alkalization in patients with tumor lysis syndrome, unsafe transportation of comatose patients with leukostasis or malignant brain/leptomeningeal infiltration, and surgical biopsies when minimally invasive tests can be used instead. Lastly, in these high-risk patients, experience from specialized centers shows that close collaboration between hematologists and intensivists ensures optimal management until the patient is sufficiently stable to be transferred to the ward for continued treatment. It should be borne in mind that an ICU bed can be used for several hours to several days, according to the need to ensure patient safety during a procedure, perform an initial evaluation, or provide life support.

9. Important unknowns (Table 5)

Several points of concern are not well addressed in the current literature and deserve further research, as well as panel discussions to develop expert opinion (Table 5). To address the ten issues listed here, collaborative studies including patients from several ICUs and countries are required, as well as benchmarking across a variety of settings. Large observational studies are needed with long-term patient follow-up and careful analyses of medical practices regarding both hematological and life-sustaining treatments.

9.1. In summary: a standard of care for critically ill patients with hematological malignancies (Fig. 4)

We must continue our efforts to improve the standard of care of critically ill patients with HMs. Admission policies should be reappraised, unrestricted state-of-the-art management provided, and effective communication between intensivists and hematologists nurtured. ICU admission should be considered for the initiation of emergent chemotherapy, chemotherapy initiation in patients at high risk for tumor lysis syndrome, and patients with tumor infiltration or compression. We must remain abreast of all diagnostic or therapeutic advances. We encourage early ICU admission to enable the use of diagnostic and therapeutic strategies that are the least invasive possible and well adapted to the clinical presentation and pathophysiological changes. We also recommend widespread use of ICU trials for patients who are not bedridden and for whom there is hope that control or cure of the disease is achievable. Some advances are ascribable to things that we no longer do, such as delaying ICU admission (Fig. 4). In the near future, multiple avenues of research will have to be traveled. We need to evaluate new diagnostic tests, new therapeutic strategies, effects of old strategies now that outcomes have changed substantially, admission policies, and new risk factors for invasive fungal infections (including ICU-related factors, in addition to chronic inflammation, sepsis, ARDS). The continuous progress that is being made warrants the hope that targeted and personalized treatments will soon be widely available to prevent disease- and treatment-related life-threatening complications.

Fig. 4. Components of the standard of care in critically ill patients with hematological malignancies.

Conflict of interest

None.

References

[1] Patel JD, Krilov L, Adams S, et al. Clinical cancer advances 2013: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 2013;32:129–60.
[2] McDermott U, Downing JR, Stratton MR. Genomics and the continuum of cancer care. N Engl J Med 2011;364:340–50.
[3] Schmatz AI, Streubel B, Kretschmer-Chott E, et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. J Clin Oncol 2011;29:1445–51.
[4] Hanahan D. Rethinking the war on cancer. Lancet 2014;383:558–63.
[5] Sant M, Minicozzi P, Mounier M, et al. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. Lancet Oncol 2014;15:931–42.
[6] Peigne V, Rusinova K, Karlin L, et al. Continued survival gains in recent years among critically ill myeloma patients. Intensive Care Med 2009;35:512–8.
[7] Khassawneh BY, White Jr P, Anaissie EJ, Barlogie B, Hiller FC. Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. Chest 2002; 121:185–8.
[8] Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. Lancet 2014;383: 2239–52.
[9] Thepot S, Itzykson R, Seegers V, et al. Azacitidine in untreated acute myeloid leukemia: a report on 149 patients. Am J Hematol 2014;89:410–6.
[10] Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol 2013;31:2810–8.
[11] Azoulay E, Mokart D, Lambert J, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 2010;182:1038–46.
[12] Azoulay E. A new standard of care for critically ill patients with cancer. Chest 2014; 146:241–4.
[13] Mokart D, Lambert J, Schnell D, et al. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. Leuk Lymphoma 2013;54:1724–9.
[14] Azoulay E, Lemiale V. Non-invasive mechanical ventilation in hematology patients with hypoxemic acute respiratory failure: a false belief? Bone Marrow Transplant 2012;47:469–72.
[15] Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001;344:481–7.
[16] Benoit DD, Soares M, Azoulay E. Has survival increased in cancer patients admitted to the ICU? We are not sure. Intensive Care Med 2014;40:1576–9.
[17] Saillard C, Mokart D, Lemiale V, Azoulay E. Mechanical ventilation in cancer patients. Minerva Anestesiol 2014;80:712–25.
[18] Pene F, Percheron S, Lemiale V, et al. Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med 2008;36:690–6.
[19] Pene F, Salluh JI, Staudinger T. Has survival increased in cancer patients admitted to the ICU? No. Intensive Care Med 2014;40:1573–5.
[20] Darmon M, Thiery G, Ciroldi M, Porcher R, Schlemmer B, Azoulay E. Should dialysis be offered to cancer patients with acute kidney injury? Intensive Care Med 2007;33: 765–72.
[21] Canet E, Lengline E, Zafrani L, Peraldi MN, Socie G, Azoulay E. Acute kidney injury in critically ill allo-HSCT recipients. Bone Marrow Transplant 2014;49:1121–2.
[22] Lecuyer L, Chevret S, Guidet B, et al. Case volume and mortality in haematological patients with acute respiratory failure. Eur Respir J 2008;32:748–54.
[23] Thiery G, Azoulay E, Darmon M, et al. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol 2005;23: 4406–13.
[24] van Vliet M, Verburg IW, van den Boogaard M, et al. Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. Intensive Care Med 2014;40:1275–84.
[25] Puxty K, McLoone P, Quasim T, Kinsella J, Morrison D. Survival in solid cancer patients following intensive care unit admission. Intensive Care Med 2014;40: 1409–28.
[26] Mokart D, Pastores SM, Darmon M. Has survival increased in cancer patients admitted to the ICU? Yes. Intensive Care Med 2014;40:1570–2.
[27] Azoulay E, Lemiale V, Mokart D, et al. Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med 2014;40:1106–14.
[28] Azoulay E, Soares M, Darmon M, Benoit D, Pastores S, Afessa B. Intensive care of the cancer patient: recent achievements and remaining challenges. Ann Intensive Care 2011;1:5.
[29] Azoulay E, Recher C, Alberti C, et al. Changing use of intensive care for hematological patients: the example of multiple myeloma. Intensive Care Med 1999;25:1395–401.
[30] Azoulay E, Schlemmer B. Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 2006;32:808–22.
[31] Lengline E, Raffoux E, Lemiale V, et al. Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure. Leuk Lymphoma 2012;53:1352–9.
[32] Song JU, Suh GY, Park HY, et al. Early intervention on the outcomes in critically ill cancer patients admitted to intensive care units. Intensive Care Med 2012;38: 1505–13.
[33] de Montmollin E, Tandjaoui-Lambiotte Y, Legrand M, et al. Outcomes in critically ill cancer patients with septic shock of pulmonary origin. Shock 2013;39:250–4.
[34] Pene F, Aubron C, Azoulay E, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. J Clin Oncol 2006;24:643–9.
[35] Afessa B, Tefferi A, Dunn WF, Litzow MR, Peters SG. Intensive care unit support and acute physiology and chronic health evaluation III performance in hematopoietic stem cell transplant recipients. Crit Care Med 2003;31:1715–21.
[36] Soubani AO, Shehada E, Chen W, Smith D. The outcome of cancer patients with acute respiratory distress syndrome. J Crit Care 2014;29(183):e7-12.
[37] Azoulay E, Thiery G, Chevret S, et al. The prognosis of acute respiratory failure in critically ill cancer patients. Med (Baltimore) 2004;83:360–70.
[38] Darmon M, Vincent F, Camous L, et al. Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Reanimation Respiratoire et Onco-Hematologique. Br J Haematol 2013;162:489–97.
[39] Buyse S, Teixeira L, Galicier L, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med 2010;36:1695–702.
[40] Schellongowski P, Staudinger T, Kundi M, et al. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with de novo acute myeloid leukemia: a single center experience. Haematologica 2011;96:231–7.
[41] des Ordons Roze, Chan K, Mirza I, Townsend DR, Bagshaw SM. Clinical characteristics and outcomes of patients with acute myelogenous leukemia admitted to intensive care: a case–control study. BMC Cancer 2010;10:516.
[42] Oeyen SG, Benoit DD, Annemans L, et al. Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: a single center study. Intensive Care Med 2014;39:889–98.
[43] Azoulay E, Kouatchet A, Jaber S, et al. Noninvasive mechanical ventilation in patients having declined tracheal intubation. Intensive Care Med 2013;39:292–301.
[44] Ho TH, Barbera L, Saskin R, Lu H, Neville BA, Earle CC. Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. J Clin Oncol 2011;29:1587–91.
[45] Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. J Clin Oncol 2012;30:4387–95.
[46] Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. J Clin Oncol 2012;30:880–7.
[47] Soares M, Caruso P, Silva E, et al. Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. Crit Care Med 2010;38:9–15.
[48] Soares M, Carvalho MS, Salluh JI, et al. Effect of age on survival of critically ill patients with cancer. Crit Care Med 2006;34:715–21.
[49] Nava S, Ferrer M, Esquinas A, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncol 2013; 14:219–27.
[50] Merceron S, Canet E, Lemiale V, Azoulay E. Palliative vasoactive therapy in patients with septic shock. Chest 2014;146:e107–8.
[51] Afessa B, Azoulay E. Critical care of the hematopoietic stem cell transplant recipient. Crit Care Clin 2010;26:133–50.
[52] Groeger JS, Lemeshow S, Price K, et al. Multicenter outcome study of cancer patients admitted to the intensive care unit: a probability of mortality model. J Clin Oncol 1998;16:761–70.
[53] Groeger JS, White Jr P, Nierman DM, et al. Outcome for cancer patients requiring mechanical ventilation. J Clin Oncol 1999;17:991–7.
[54] Burghi G, Lemiale V, Seguin A, et al. Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis. Intensive Care Med 2011;37: 1605–12.
[55] Blot F, Guiguet M, Nitenberg G, Leclercq B, Gachot B, Escudier B. Prognostic factors for neutropenic patients in an intensive care unit: respective roles of underlying malignancies and acute organ failures. Eur J Cancer 1997;33:1031–7.
[56] Darmon M, Thiery G, Ciroldi M, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. Crit Care Med 2005;33:2488–93.
[57] Benoit DD, Depuydt PO, Vandewoude KH, et al. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. Intensive Care Med 2006;32:93–9.
[58] Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. Crit Care Med 2007;35:808–14.