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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].

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

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.