Review Article

Prognostic factors in cancer patients in the intensive care unit

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Abstract

Intensive care has become important for the treatment of patients with cancer. However, the prognosis of these patients is considered poor a priori and decisions to admit a patient with cancer to the intensive care unit (ICU) are still source of controversy between oncologists and intensivists. The outcome of severely ill cancer patients does not depend solely on the causes that determine the admission to the ICU, but it also depends on cancer- and anticancer-related characteristics, such as performance status and cancer status. The decision-making process of ICU admission and of the appropriateness of advanced life-support requires a thorough evaluation of these characteristics and of the expectancies and wishes of patients and family members. A better understanding of such parameters may be helpful to avoid forgoing intensive care to patients who can potentially benefit from it.

Key words: Acute respiratory failure, cancer, intensive care, outcome, prognostic factors

Introduction

Cancer is increasing major cause of morbidity and mortality worldwide.[1-3] The number of new cases of cancer in the world estimated for the year of 2020 will be more than 15 million, with deaths increasing to 12 million. It is also expected the burden of cancer in terms of incidence, morbidity and mortality will be substantially more severe in developing countries than developed ones.[3] However, over the last decades advances in cancer treatment were translated into enhanced possibilities of cure or disease control as well as improved survival and quality of life.[1,2] As consequence, intensive care has become essential for cancer patients and most institutions that care for these patients have an intensive care unit (ICU).[4,5]

The main reasons for admission to the ICU are 1) postoperative care after major surgical resections, 2) severe cancer or chemo-radiation-related complications and 3) concurrent severe acute illnesses.[4,5] Usually, patients are admitted to the ICU when they have a malignancy with a reasonable chance of cure or control and, especially, if the acute illness is potentially reversible. Patients' wishes and personal values must be respected regarding decisions to initiate and to forgo life-sustaining therapies as well as those related to the appropriateness of aggressive therapy as invasive mechanical ventilation, dialysis and cardio-pulmonary resuscitation.[5,6] Nevertheless, the admission of patients with cancer to the ICU is still a matter of substantial controversy among oncology consultants and the ICU team. The prognosis of these patients is usually considered dismal a priori. This inappropriate notion is responsible for a considerable part of the ICU refusals of patients with cancer, especially in general hospitals. Moreover, these decisions are frequently stained by prejudice since patients without cancer, but

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suffering from chronic diseases with similar prognoses, have better chances of being admitted to the ICU and receiving advanced life-support compared to patients with cancer.[7,8] On the other hand, with the institution of full code, prolonging the life of patients with dismal chances of recovery may result in plain medical futility. This situation imposes a heavy burden of suffering and frustration to the patient and his beloved ones as well as the ICU team. Additionally, the ever-growing cost of intensive care and the limited availability of ICU beds lead us to consider suitably on the rationing of resources.[9,10]

Briefly, the evaluation of the appropriateness of admitting a patient with cancer to the ICU should be supported by a better knowledge of a complex array of clinical factors related to the acute illness, cancer characteristics and patients`/families' expectations. This is even more important if we acknowledge that the mortality of critically-ill patients with cancer is substantially higher than of non-cancer patients.[11-14]

This article reviews the main aspects related to the evaluation of the prognosis of critically-ill patients with cancer. Studies were selected through a careful search in the Medline database accessed by Pubmed (www.pubmed.gov) in February 2007. Descriptors were: cancer, outcome, mortality, intensive care organ dysfunction and mechanical ventilation. Other references were also individually included after the initial search.

The Use of Prognostic Scores

Severity of illness scores has been extensively used in the evaluation of the prognosis of critically-ill patients. Despite lacking the ability of predicting individual outcome,[15] prognostic scores may be useful in prognostic discussion, improvement of resource allocation, stratification for clinical trials and evaluation of the quality of ICU services.[16] General scores usually have a poor performance in critically-ill patients with cancer due to inadequate calibration and underestimation of mortality.[17-24] The limitation of the general scores lead to the development of an specific score for acutely ill patients with cancer, the cancer mortality model (CMM).[20] The CMM uses variables related to physiologic derangements and also performance status, evidence of disease progression or relapse and treatment with allogeneic bone marrow transplant (BMT). However, the CMM performance was not superior to those of general scores.[21-23] Recently, we have validated the SAPS 3 admission prognostic model in patients with cancer in need of intensive care.[25] Although, we have found a good performance for this new prognostic model in that single-center study, additional studies are necessary.

Severity of Illness, Acute Organ Dysfunctions, Mechanical Ventilation and Renal Replacement Therapy

The severity of acute physiologic derangements and acute organ dysfunctions are the main predictors of short-term mortality in critically ill patients with cancer.[11,14,17,26-32] Acute respiratory failure (ARF) with the need of invasive mechanical ventilation (MV) is usually associated with a poor outcome.[14,20,21,28,30,32-34] Until recently, mortality rates in patients with cancer and respiratory failure were typically higher than 75%.[10,27,35-37] However, in the last decade, significant improvement in the outcomes of cancer patients with ARF was observed;[11,28,29,38,39] a major change that was ascribed to the application of low-tidal volume ventilation[40] and the use of noninvasive ventilation (NIV) in immunosupressed patients[41] and acutely ill cancer patients.[42] In the studies of Hilbert *et al*[41] and Azoulay *et al*[38] patients treated initially with NIV had significantly lower mortality rates as compared to those treated with conventional MV (50% vs. 81% and 44% vs. 71%, respectively). Yet, many patients are admitted to the ICU with severe respiratory derangements or too late in the course of their acute disease limiting the use of NIV.[29,39] Early identification of respiratory distress and good patient selection is essential to augment the benefits of NIV.[38,41] Conversely, the recognition of early signs of NIV failure is crucial as prolonging NIV in patients who require subsequent endotracheal intubation is associated with a worse outcome as compared to patients who received conventional MV as a first choice of therapy for ARF.[42,43] Even in patients with lung cancer in whom ARF is considered a terminal complication, the prognosis of seems to be improving. In a recent cohort of 143 patients with lung cancer admitted at two ICUs because of severe acute medical illnesses, MV was used in 100 patients and overall hospital mortality was 59%.[44] It is important to stress that among these 100 ventilated patients only 13 were initially treated with NIV.

Acute kidney injury (AKI) is also a common complication in patients with cancer and may occur as consequence of multiple causes, such as of the cancer itself (myeloma

kidney, urinary tract obstruction), its treatment (acute tumor lysis syndrome, drug induced nephropathy) and associated severe complications (sepsis, hypercalcemia). AKI is associated with a worse prognosis and can impose limitations to the institution of the appropriate regimen of chemotherapy. In addition, in critically-ill patients with cancer, AKI usually occurs in the context of multiple organ dysfunctions and is associated with high mortality rates,[45-48] raising concerns on the appropriateness of renal replacement therapy (RRT), its timing and method of choice. Moreover, AKI was independently associated with longer duration of weaning from MV.[48] In a recent cohort of 309 patients with cancer and AKI, older age, poor performance status, cancer recurrence or progression and the severity of organ failures were independently associated with increased mortality.[46] The timing of institution of RRT seems to be an important issue to take into account as there were no survivors among patients in whom RRT was initiated after the fourth day of ICU admission.[46] In the study of Darmon *et al*[45] the deterioration of kidney function with the need of RRT after the first day ICU stay was the main predictive factor for hospital death.

Age, Performance Status and Comorbidities

Life expectancy is increasing globally.[49] According to the World Health Organization report " between 1970 and 2025, a growth in older persons of some 694 million is expected and in 2025, there will be a total of about 1.2 billion people over the age of 60".[49] Considering that elderly patients are the main users of the health system, such demographic changes will have clear impact on the allocation of resources and public health policies.

Ageing is associated with the reduction of physiologic capacity and with higher prevalence of chronic diseases including cancer. The impact of age on the mortality of critically-ill cancer patients remains controversial.[14,20,27,29,30,33,34,50] However, the interpretation of these results should be done with caution, as selection bias on ICU admission is inherent to the triage process. In a study of our group, age was an independent prognostic factor.[50] Nevertheless, the overall effect of age on the six-month survival was modest, but the impact of other covariates such as performance status and comorbidities on the outcomes was higher in elderly patients.[50] Regrettably, while age should not be the sole determinant of ICU refusal,[51] elderly patients still have a higher probability of refusal of ICU admission[52] and of having decisions to forgo life-sustaining therapies.[53]

The performance status is routinely used to evaluate the functional capacity and autonomy in patients with cancer. A compromised performance status (Karnofsky < 70 or Eastern Cooperative Oncology Group scale 3-4) before hospital admission was associated with increased short and long-term mortality rates in ICU patients with cancer.[20,29,30,50,54]

Patients with cancer often present with severe comorbidities that may have implications in their outcomes.[55,56] The presence of comorbidities significantly increases the risk of complications related to chemotherapy and other anticancer therapies, which may impose limitations to the administration of them.[56] Available data about the impact of comorbidities on the prognosis of critically-ill patients with cancer are scant. A single study has focused on the use of comorbidities indexes in this patient population.[30] In that study, 50% of the patients had comorbid conditions and the presence of severe comorbidities evaluated by the adult comorbidity evaluation (ACE-27) was independently associated with six-month mortality. Moreover, the ACE-27 was a better instrument to measure comorbidities in critically ill patients with cancer than the Charlson comorbidity index.[30]

Cancer-related Characteristics

The diagnosis of cancer encompasses a wide array of diseases with diverse clinical characteristics and biological behavior. Designing studies to evaluate specific groups of critically ill patients with cancer is a difficult task. Traditionally, patients have been grouped in two large categories: solid tumors and hematological malignancies. Solid tumors are usually staged according to disease extension as locoregional or metastatic disease. Conversely, the classification and staging of hematological malignancies is much more complex; most authors choose to separate them into large categories as multiple myeloma, Hodgkin's disease, leukemia and non-Hodgkin's lymphoma.[14,17,30,36,57] BMT patients are usually studied in separate regardless of the primary site of cancer, as they have significant peculiarities and are usually classified in two groups according to the type of BMT procedure (autologous or allogeneic).[18,27,57] BMT patients admitted to the ICU remain a population with

exceedingly high mortality rates (>85%), especially in case of allogeneic BMT, despite a slightly better prognosis observed in recent years.[11,20,27,36,57]

Until recently the outcomes of patients with neutropenia and hematological malignancies were considered grim especially in the setting of ARF in need of MV.[27,35,37] However, recent studies have observed that neither the type of cancer nor the presence of neutropenia were associated with worse outcomes and might have lost their impact on the mortality.[11,14,29,30,33,38,57] The rational use of granulocyte colony stimulating factors have reduced both the risk and duration of neutropenia in patients receiving chemotherapy[58] and early recovery of the neutrophil count is associated with better prognosis.[34] Moreover, starting chemotherapy in the ICU can be life-saving to patients with a first presentation of a malignancy when infection or organ failure is present.[32,59] However, on the other hand, disease recurrence or progression (of either solid or hematological malignancies) is a key predictor of mortality.[20,27,29,30,44,50,57]

Quality of Life

Ideal prognostic evaluation has to be based on multiple aspects including health-related quality of life (HRQOL) and those related to self-perception of quality of care. Symptoms of pain, stress, insomnia, depression and anxiety are frequent in patients who survive from critical illnesses[60,61] and its main long-term consequences are the reduction of functional capacity and of the ability of working and socializing. Perhaps as a consequence of its "stigma" of a serious and often fatal disease, cancer studies evaluating prognosis have usually focused on mortality as the main outcome variable. Only few years ago, Nelson *et al*[62] observed the occurrence of painful or distressful experiences in up to 75% of patients admitted to the ICU. Data on HRQOL are also scarce. Yau *et al*[63] studied 92 critically-ill patients with hematological malignancies and observed that most of the survivors perceived their HRQOL as good one year after ICU admission. However, further studies are urgently needed.

Conclusions

The evaluation of prognosis is essential for the clinical care of ICU patients and for the appraisal of the impact of new therapeutic interventions. It is also crucial to expand the current knowledge on the prognosis of critically-ill patients with cancer by studying longer follow-ups, specific patient populations, incorporation of multidimensional methods of evaluation and HRQOL. The knowledge of characteristics associated with prognosis may be of assistance in the clinical decision-making process and in informing patients and family members. According to expert opinions, patients should be admitted to the ICU when clinicians are unsure of their prognosis and the consequence appropriateness of advanced support. In this case, full code should be applied for a short period (three to five days) after which the patient will be re-evaluated.[64,65] The course of organ failures and response to therapy will be considered in deciding for the maintenance or withdrawal of support after a careful discussion involving oncologists and patient's family.It is essential to re-emphasize that no single characteristic or score should be used to predict prognosis on individual basis and as a sole parameter for ICU triage procedures. The most important aspect should be not to refuse intensive care to those who might potentially benefit from it.

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