

Deciding intensive care unit-admission for critically ill cancer patients

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Abstract

Over the last 15 years, the management of critically ill cancer patients requiring intensive care unit admission has substantially changed. High mortality rates (75-85%) were reported 10-20 years ago in cancer patients requiring life sustaining treatments. Because of these high mortality rates, the high costs, and the moral burden for patients and their families, ICU admission of cancer patients became controversial, or even clearly discouraged by some. As a result, the reluctance of intensivists regarding cancer patients has led to frequent refusal admission in the ICU. However, prognosis of critically ill cancer patients has been improved over the past 10 years leading to an urgent need to reappraise this reluctance. In this review, the authors sought to highlight that critical care management, including mechanical ventilation and other life sustaining therapies, may benefit to cancer patients. In addition, criteria for ICU admission are discussed, with a particular emphasis to potential benefits of early ICU-admission.

Key words: Critically ill patients, oncology, intensive care, admission refusal, prognosis

Over the last 15 years, the management of critically ill cancer patients requiring intensive care unit (ICU) admission has substantially changed.^[1-3] High mortality rates (75-85%) were reported 10-20 years ago in cancer patients requiring life sustaining treatments, especially when mechanical ventilation was needed^[4-6] or in recipients of hematological stem cell transplantation.^[7]

Because of these high mortality rates, the high costs and the moral burden for patients and their families, ICU admission of cancer patients became controversial^[8,9] or even clearly discouraged by some authors.^[10] As a result, the reluctance of intensivists regarding cancer patients has led to frequent refusal of admission in the ICU.^[11] However, prognosis of critically ill cancer patients

has been improved over the past 10 years leading to an urgent need to reappraise this reluctance.^[2,3,12-15]

In this review, the authors seek to highlight that critical care management, including mechanical ventilation and other life sustaining therapies, may benefit cancer patients. In addition, criteria for ICU admission are discussed, with a particular emphasis to potential benefits of early ICU-admission.

Improvement of Prognosis of ICU Cancer Patients: The evidence

Three factors have contributed to this trend. First advances in the treatment of solid tumors and hematological malignancies have led to a decreased mortality rates. These advances include availability of new drugs, as well as intensified treatment protocols and improvement of supportive care. In patients with non Hodgkin lymphoma and other lymphoproliferative disorders, the adjunction of rituximab to conventional chemotherapy^[16] demonstrated

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dramatical improvements in terms of event free survival. Similarly, the use of Imatinib in patients with chronic myeloid leukemia resulted in better outcomes and lower need for hematopoietic stem cell transplantation.^[17] Along this line, in patients with multiple myeloma, thalidomide and bortezomib provided substantial benefits in terms of survival.^[18] As a consequence, survival increased by 20% over the last two decades.^[19] Intensive care physicians must be aware of these therapeutic advances, which have considerably modified the course of several malignancies. We believe that a decision to admit cancer patients to the ICU must take into account this important data as to avoid losing a chance for the patients.

Second, improvement in diagnostic and therapeutic strategies in critically ill patients have led to better management of specific ICU diseases. Early and aggressive management of septic shock have led to decreased mortality rates in both cancer patients^[20] and non cancer patients.^[21] Noninvasive strategies have been implemented in patients with acute respiratory failure, for both diagnostic procedures and noninvasive ventilation.^[1,22,23] Improvement in the management of specific critically ill cancer patients such as acute tumor lysis syndrome and acute respiratory failure will be developed in this issue of the Journal.^[24]

Third, efforts have been made in order to identify patients who are likely to benefit from ICU admission^[11] and to improve triage of cancer patients referred to the ICU. A prospective longitudinal study performed in France in 2001 showed that cancer patients were at high risk to be refused admission.^[25] However, more recently, a national Swiss survey about admission to intensive care showed that doctors do not discriminate against cancer when deciding on admission to the ICU, suggesting that doctor's perception of therapeutic options for malignancies may be changing.^[26]

However, decision to admit or refuse ICU admission for cancer patients remains a difficult decision based on complex criteria, including objective and subjective data.^[25] It should be reminded that classic predictors of mortality (neutropenia, physiological severity, autologous stem cell transplantation) are no longer relevant and should not be used to base a decision of ICU admission.

Pitfalls in the Use of Scoring Systems

Different scoring systems such as the acute physiology and chronic health evaluation (APACHE) II or III,^[27] simplified acute physiology score (SAPS II)^[28] or mortality probability models II (MPM II)^[29] have been developed to predict outcome of critically ill patients admitted to the ICU. They have all been constructed for the general population and are not accurately calibrated to predict mortality in critically ill cancer patients, tending to under estimate the mortality.^[30-32] Specific cancer scoring system have been proposed, but does not seem to have any advantages over the general prognostic models,^[9,33,34] partly because they are based on heterogeneous population of medical and surgical patients with solid tumors or hematological malignancies. Consequently, these prognostic scores are not accurate enough to be used in routine management and none of them can be recommended to help the intensivist at the bedside.

Classic Predictors of Death are no Longer Relevant

Underlying malignancy

In the decision making process of ICU admission of cancer patients, the prognosis of the underlying malignancy is frequently considered. However, the respective influences of the severity of both the underlying disease and the acute illness on patient's outcome have to be clearly separated.

In a series of patients with hematological malignancies, Massion *et al*, evaluated the ICU and in-hospital prognosis according to the patient's long term prognosis.^[13] Patients were separated in three groups according to the estimated three year prognosis: good, intermediate or poor if their three-year survival probability was >50%, 20 to 50%, of <20%. Neither ICU nor in-hospital mortality was correlated with long-term prognosis, but there was a strong association between short-term prognosis and acute organ dysfunction. Consequently, the reluctance to admit patient with hematological malignancies based on the prognosis of the underlying malignancy is no longer justified. Obviously, this is in relation with a previous triage performed by hematologists and oncologists. Also, this cannot apply to patients with advanced malignancies and short-term predicted survival (i.e., life expectancy <

6 months for some authors), in whom ICU admission is not justified.^[13]

Neutropenia

Because of their increased risk for severe bacterial and fungal infections, neutropenic patients are exposed to life-threatening complications. Based on the literature published over the last 20 years, neutropenia is considered to be associated with poor prognosis in critically ill cancer patients. However, several studies have shown that neither the neutrophil count,^[9,35,36] nor neutropenia duration^[36] were associated with prognosis. Similarly, Regazzoni *et al*, recently showed in a series of cancer patients admitted to the ICU for septic shock, that both neutropenic and nonneutropenic patients had similar outcomes in terms of mortality and length of stay in the ICU, compared to patients with normal neutrophil count.^[37] In these studies and the study by Blot *et al*, outcomes were related to the severity and the number of organ failures.^[9,15,30,35,37] Consequently, neutropenia, even when prolonged, should not be taken into account in the decision to admit or refuse admission to an intensive care unit. Moreover, the care of neutropenic patients in the ICU should not be different from the critically ill cancer patients with normal leukocyte count.

Hematopoietic stem cell transplantation

Similarly to neutropenia, allogeneic hematopoietic stem cell transplantation (HSCT) has been associated with bad prognosis when patients experienced life-threatening complications. Several studies reported mortality rates of 85-90% when mechanical ventilation was required^[38-41] and 100% if the mechanical ventilation was associated with hemodynamic instability, renal failure or hepatic failure, suggesting that life sustaining treatments should be discontinued in these patients.^[7] However, recent studies have highlighted this issue and have allowed intensivists to a reappraisal. Until recently, all the studies evaluating HSCT pooled patients receiving autologous and allogeneic HSCT. This led to confusion in the results because of major differences between the two procedures: allogeneic HSCT involves immunological conflict between donor's hematopoietic stem cells and host, which results in graft versus host disease (GVHD) and deep immunodeficiency, whereas autologous HSCT only involves intensive chemotherapy and infusion of the own patient's stem cell with no immunological conflict. Since prognosis of life-threatening complications in

autologous and allogeneic HSCT is widely different from one another, caution is needed when analyzing studies which pool both types of patients.

Along this line, in the study by Kassawneh *et al*, homogeneous patients with autologous HSCT who required mechanical ventilation were analysed.^[3] The authors reported an improvement of the prognosis over time and a 35% hospital survival rate, suggesting that ICU admission was not futile. The authors concluded that patients undergoing autologous HSCT should be considered and managed as patients with hematological malignancy and chemotherapy.

Conversely, a recent study from Pene *et al*, reported 209 patients with allogeneic HSCT admitted to three French ICUs.^[42] Among them, 122 patients required mechanical ventilation. The overall in-ICU, in-Hospital and six-month survival rate in mechanically ventilated patients were 18%, 15.6% and 14%, respectively. Mechanical ventilation, vasoactive drugs, corticosteroid treatments and high bilirubin levels were independently associated with mortality, whereas interval time from HSCT and ICU < 30 day was associated with survival. The conclusion was that ICU admission, mechanical ventilation and maximal organ support may be justified in patients at the early stage of allogeneic HSCT, but should be discouraged in patients treated with corticosteroids for GVHD.

Chemotherapy in the ICU

Some patients are presenting with newly diagnosed malignancies and acute life-threatening complications requiring admission to an ICU. The main disorders are infection and organ involvement by cancer, such as pulmonary leukemic infiltration, central nervous system involvement, bulky mediastinal tumor, hemophagocytosis or tumor lysis syndrome. In these patients, the prompt control of the malignancy is the only way of ensuring recovery and immediate cancer chemotherapy has to be initiated in the ICU in addition to usual life-sustaining interventions. We recently reported 100 patients who underwent cancer chemotherapy in the ICU for newly diagnosed malignancies, in whom survival rate was 60% and 49% at 30-days and six-months respectively.^[15] As reported in the majority of the studies, factors independently associated with mortality were related to organ failure: need for vasopressors, mechanical

ventilation and liver failure. Among the 54 patients requiring endotracheal mechanical ventilation, 19 survived at day 30 (35%). This study highlighted the feasibility of cancer chemotherapy in the ICU, along with organ failure and life-sustaining therapies.

Appropriateness of the Decision to Refuse Admission

Definite criteria to ensure whether admission to the ICU is appropriate are often lacking at the bedside. Inappropriate admission of patients to the ICU may lead to inadequate utilisation of medical resources and futility. On the opposite, inappropriate denial for admission of a patient to the ICU may result in the worsening of life-threatening conditions and increase the risk of death. We evaluated the appropriateness of ICU refusal in a prospective longitudinal study over a one-year study in our hospital.^[11] All patients for whom admission was requested were followed-up during six months, regardless of whether admission was granted or not. Our results showed that errors in judgement by the intensivist who decided to refuse admission were frequent and may translate into increased mortality for the patients.^[11] Thirty-day mortality was 21.6%, for patients who were refused admission because they were considered too well to benefit from ICU admission and 74% for patients who were refused admission because they were considered too ill to benefit from ICU admission. These results show the inaccurate clinical judgement by intensive care physicians for both patients considered too well or too sick to benefit and suggest that tools are lacking to the intensivist at the bed side and at the time of ICU proposal, to discriminate which patients are likely to benefit from ICU admission.^[11]

We suggest the following admission policy for ICU admission: first, patients with poor performance status and with no cancer treatment options should not be considered for ICU admission; second, a broad policy of admission to the ICU can be considered, with the aim to avoid inappropriate ICU refusal.

Serial Evaluation of Organ Dysfunction: The Key for Prognostic Evaluation

As frequently reported, the main determinants of mortality in critically ill cancer patients are the severity and the number of organ failures.^[13,15,20,30] Blot *et al*, evaluated the prognosis of neutropenic patients according

to organ failures present at ICU admission.^[30] Mortality rate of patients with one, two or three organ failures was 40%, 60% and 90% respectively and among all the organ failures, respiratory failure requiring mechanical ventilation has the strongest effect of outcome. Other studies in nonneutropenic patients reported similar results but with better outcomes. Mortality rates ranged from 18% to 75% in patients with 1 to 5 organ failures admitted to the ICU with newly diagnosed malignancies.^[15] However, although organ dysfunction is the cornerstone of the evaluation of patient's severity, data available on admission cannot accurately discriminate between patients who are likely to survive and others.^[20,30] In this regard, the course of organ dysfunction over the first days of life-sustaining treatment seems to be of critical value to predict outcome. In patients with hematological malignancies, the loss of two or more organ failures at day five was associated with 29% 30-day mortality rate, whereas patients in whom the number of organ dysfunction did not decrease or increased had a 81% 30-day mortality rate.^[13] Moreover, time from admission to initiation of vasopressors, mechanical ventilation or renal replacement therapy seems to be highly correlated to prognosis. Thus, in a recent study including 108 critically ill cancer patients with at least 2 organ failures, we found no survivors among patients in whom mechanical ventilation, vasopressors or renal replacement therapy was initiated after day three.^[43,44] These results suggest that organ failures occurring in the course of the ICU stay have more influence on the outcome than organ failures present at admission. Consequently, the course of organ failures over the first days of full life-sustaining treatment could be a simple and objective tool for intensivists to identify patients who are likely to die and those who are likely to survive. Patients in whom the number and severity of organ dysfunction are decreasing are likely to survive and may benefit from the continuation of aggressive care. By contrast, patients in whom organ failures does not decrease or patients who experience new organ dysfunction within the first days of intensive care, should be discussed for withdrawal or withdrawing of life sustaining therapies.^[43,44]

Because data available at ICU admission are not accurate enough to predict prognosis and since patients with no hope for survival are easy to identify after an "ICU trial", we suggest a strategy based on broad ICU admission, life-sustaining treatment for few days and daily

evaluation based on organ failures.

This strategy, which is an alternative to ICU refusal in high severity patients, allows clinicians to better appraise the prognosis and relieves families from guilt due to a perception that nonadmission leads to loss of chance. Of course, patients with cancer for which potentially no lifespan-extending treatment is available or who are bedridden should not be admitted to the ICU and should be excluded of this approach.

Nevertheless, this strategy might be associated with an increased proportion of deaths occurring after treatment-limitation decisions. This may translate into increased burden on the nurses and physicians and into a higher rate of conflicts.^[44]

Early ICU Management in Low Severity Patients

Beside evaluation of patients with low severity is also inaccurate.^[11] In our series, 21% of patients who were refused admission because of lack of severity died before day 30, suggesting that ICU admission might have been inappropriately denied. Since all of these patients were finally admitted less than 24h after the initial proposal, one can hypothesise that the delay before ICU admission might have influenced the patient's prognosis. That point has been raised by Sprung *et al*, in non cancer patients, who reported higher mortality rates in patient later admitted, compared to patients rapidly admitted to the ICU.^[45] Therefore, early identification of patients who need to be carefully monitored or patients at risk to develop organ failure is an important issue. In a recent study, 53 patients with hematological malignancies who developed pneumonia have been followed-up from the onset of the pneumonia.^[46] Approximately half of them (45%) required transfer to the ICU. Simple factors, such as the need of more than 3L/min of O₂ supplementation to achieve SpO₂>92% and more than one quadrant involved at the time of onset of the pneumonia were highly associated with ICU admission. Predictive value of more than 3L/min of supplemental O₂ to achieve SpO₂>92% at the onset of the pneumonia has a positive predictive value of transfer to the ICU of 95%. The authors did not recommend that hematologists should decide a transfer to the ICU at this value, but that these patients should be carefully monitored. The interesting point of this study is that the cut off value of 3L/min is usually too low to require a transfer to the ICU.

Therefore, in patients with hematological malignancies, low severity of organ failures could be interpreted as predictor of further deterioration. Early transfer to the ICU should be discussed for these patients.

In this regard, good co-operation between onco-hematologists and intensivists is the cornerstone of early identification and management of these patients. A recent survey performed in 10 French hospitals, onco-hematologists and intensivists were asked about the criteria upon which they commonly base their decision to refer or to admit cancer patients to the ICU. Sixty-three per cent of the intensivists appreciate to admit patients early in the course of organ failure, compared to 32% of the onco-hematologists.^[47]

Conclusion

Over the last decade, outcome in cancer patients admitted to the ICU has improved. Classic predictors of outcome of critically ill cancer patients are no longer relevant. We suggest a three-step decision making process for deciding ICU-admission in cancer patients. First, our policy discourages ICU-admission in uncontrolled malignancies and no therapeutic option available for cancer treatment; in bedridden patients or those who underwent allogenic bone marrow transplantation complicated by active GVHD. Second, ICU-admission should be unlimited in patients with newly diagnosed malignancies. Last, in all other patients, an ICU trial should be considered. It consists in an unlimited level of care for a limited time period after which serial evaluation of organ dysfunctions might provide a more accurate estimation of survival than at admission. In low severity patients, future research should identify the adequate place for patients with only one organ failure, but potentially subsequent deterioration.

Good cooperation and communication between oncologists and hematologists is the cornerstone for such approach.

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