Journal of BUON **13:** 469-478, 2008

REVIEW ARTICLE

The critically ill patient with cancer - indications for Intensive Care Unit admission and outcomes

N. Markou[1], E. Demopoulou[1], P. Myrianthefs[2]

[1]Intensive Care Unit – B, KAT Hospital, Athens; [2]Athens School of Nursing, ICU at KAT Hospital, Athens, Greece

Summary

Critically ill cancer patients admitted to the Intensive Care Unit (ICU) have high mortality rates compared to non-cancer patients. Yet, with suitable patient selection, improved ICU- and 6-month survival has been observed in these patients: admission of cancer patients to the ICU can no more be considered futile. As a general rule, patients with good performance status, who are at the initial phase of their malignant disease and with life-extending treatment options available, should be routinely admitted to the ICU, while patients being only in palliative care should not. When in doubt, an ICU trial with re-appraisal at 3-6 days may be the best policy, as the data available when ICU admission is considered, are not sufficient to identify patients who are likely to benefit from ICU management.

Key words: cancer, critical illness, ICU admission, outcome

Introduction

In the last few years, advances in oncology have resulted to an improved prognosis and extension of survival in cancer patients [1]. At the same time, the introduction of new and intensified treatment protocols, together with advanced supportive therapy for these patients, have resulted to an increasing number of disease- or therapy-associated complications, demanding ICU treatment. Improving prognosis of cancer patients has been associated with increased demand for critical care resources, which in turn has fuelled a discussion on the indications for ICU admittance for the oncological critically ill patient [2,3]. We will discuss the outcome of critically ill cancer patients admitted to the ICU as well as suggestions for ICU triage.

Outcomes of critically ill cancer patients admitted in the ICU: a changing picture?

According to established recommendations, a patient should be admitted to the ICU when there is: a) a severe, potentially life-threatening disease; and b) there is at least some chance for survival [4]. Cancer patients are usually admitted to the ICU a) for complications due to malignant disease; b) for complications of treatment (chemotherapy, hematopoietic stem cell transplantation (HSCT), postoperative monitoring and postoperative complications); c) infections [5,6]. These patients seem to have a much worse in-hospital [7-11] and long-term outcome compared with non-cancer patients admitted to the ICU [5,12]. Furthermore, critically ill cancer patients, even if they survive hospitalization, often spend only a minimal amount of time at home before dying and this limited survival is achieved at considerable cost and much suffering [13].

Most studies from the 1980s and early 1990s agree that critically ill cancer patients who required life-sustaining treatments (catecholamines, renal replacement therapy/RRT, mechanical ventilation/MV) have very low survival rates (< 20%), which are further aggravated in the presence of neutropenia or bone marrow transplantation (BMT) [13-22]. Some series reporting encouraging survival rates [23-25] included many patients admitted to the ICU solely for monitor-

Correspondence to: Dr. Nikolaos Markou. 24, Scholiou Street, 153 42 Agia Paraskevi, Athens, Greece. Tel: +30 210 6000 289, +30 6973 404 627, E-mail: nikolaos_markou@hotmail.com

Received 04-02-2008; Accepted 29-03-2008

ing and / or administration of special treatments or new therapeutic modalities, while most of those in need of life-sustaining therapies still had a bad outcome [24,25]. Thus the widespread opinion that ICU admission [26] or prolonged ICU care [18,27,28] of critically ill cancer patients should be viewed with caution, seems understandable.

On the other hand, studies from 1999 onwards suggest better outcomes of critically ill cancer patients admitted to the ICU, with ICU mortality now varying from 23 to 57% and a 6-month mortality of 33-66% [5,6,29-35]. Several studies in the last decade, confirm that over the years there has been a steady improvement in the outcomes of critically ill cancer patients [27,36-40]. Thus, according to Azoulay et al., mortality in 1990-1995 was significantly higher compared to 1996-1998 and hospitalization before or after 1996 was an independent predictor of outcome [36]. Similar findings have been reported in HSCT patients [27,40] or in cancer patients with septic shock [37]. Such improvements have been attributed to several factors: a) improved triage, with denial of admission in patients with poor functional status and underlying comorbidities, as well as in patients with no available treatments for their underlying medical conditions [29,36,40]; b) more effective treatment of some complications in critically ill cancer patients (e.g. non-invasive positive pressure ventilation/NIPPV) for acute respiratory failure) [36,41-44]; c) advances in haematology/oncology [1]; d) improvements in ICU outcome for disorders like acute respiratory distress syndrome (ARDS) or sepsis, in the general ICU patient [39,45,46]. Nevertheless, intensivists remain reluctant to admit cancer patients to the ICU [47,48].

Thus it becomes important to try identifying subgroups of patients in whom ICU admittance is warranted, as well as patients for whom refusal of admission or limitation of life support after ICU admission is justified. One group for which ICU admission seems to be unquestionably justified consists of cancer patients admitted to the ICU for postoperative care. In this group, ICU survival exceeds 80% whereas long-term survival can also be considerable [6,30,49-51].

Predictors of outcome among critically ill cancer patients

The steady improvement in ICU mortality has been accompanied by a redefinition of variables affecting survival [5,6,29,30,34-37,40,49,52-54].

Although there is no unanimity [55], most recent studies confirm that neutropenia, despite carrying a higher mortality rate [42], is no more an independent predictor of bad outcome [5,6,34,35,52,54,56]. On the other hand, neutropenia prolonged for more than 30 days is nearly always fatal [57].

Critical illness after BMT, although still associated with very high mortality rates, is no longer an independent predictor of bad outcome in many studies [5,6,29,53,58,59]. In particular, autologous BMT and "non-myeloablative" stem cell transplantation seem to have little influence on the outcomes of ICU management [40,59].

ICU survival is also independent of the characteristics of the underlying malignancy (type, stage of disease), although after recovery from complications, characteristics related to the neoplastic disease retrieve their independent influence on further survival [31,49,53,55,58,60,61]. Recurrence or progression of cancer was independently associated with hospital mortality in the study of Soares et al. [35], while Groeger et al. did not find a significant difference in outcome between newly diagnosed patients with cancer and patients with recurrent or progressive disease [62].

The effects of age on the outcome of these patients are a matter of debate [5,6,25,34-36,49,53,54,58,62]. Recently, Soares et al. in a very large study with 862 patients in an oncologic ICU concluded that age was independently associated with increased hospital and 6-month mortality (but not ICU mortality), especially with age over 60 years [63].

Poor performance status is also independently associated with increased mortality [35,60,62,64,65]. Patients needing major assistance or bedridden have a significantly higher hospital mortality (80%) with an odds ratio (OR) of 2.51 compared with ambulant patients [35].

Significant differences have been reported between survivors and non-survivors in physiological scoring systems (APACHE II, SAPS II, MPM0) on admission and some studies even report that these scores are independently associated with outcome [6,29,66-71]. Yet, these general prognostic models uniformly underestimate the likelihood of hospital mortality in critically ill oncological patients and they cannot be used to predict the outcome of an individual patient [40,52,72,73]. No major difference has been observed between APACHE II and SAPS II [36] while SAPS 3 seems to be slightly superior to SAPS II [70]. The limited usefulness of scoring systems should be attributed to the following factors: a) These scores are intended for evaluating patient groups and they do not perform well in the individual patient; b) although they have been validated in cancer patients, their calibration and

discrimination for predicting survival are poor in this subset of patients; c) they were constructed based on patients who have been effectively admitted to the ICU and these results cannot be extrapolated to patients in the emergency department or wards [72,73]. A specific oncological scoring system, the Intensive Care Mortality Model (ICMM) was developed in 1998 [70] and further refined in 2003 [74]. This system incorporates not only physiological data but also disease-related variables (allogeneic BMT, recurrent or progressive cancer) and performance status before hospitalization. ICCM had a good discriminating ability in several studies [62,73,75], but not in others [76]. A large study by Soares et al. compared 6 severity of illness scores in 562 critically ill cancer patients, excluding scheduled surgical patients. General scores significantly underestimated mortality while ICMM tended to overestimate mortality [73]. No score is accurate enough to be used for triage of individual cancer patients [72,73].

Several studies suggest that the nature and number of organ failures and the need of life sustaining therapies (mechanical ventilation, vasopressors, renal replacement therapy) are the most reliable independent predictors of outcome on admission [49,52,64, 66,77,78]. Furthermore, similar to what has been observed in the overall ICU population [79-81], changes in the number of organ failures during the first ICU days are even better correlated with survival in the critically ill cancer patient. In these patients the course of organ dysfunction in the first few days in the ICU (3rd to 5th day, depending on the study) greatly improves the prediction of outcome [27,37,53,66,67,82]. When new organ failures develop after the 3rd day or when organ failures present on admission fail to improve within 3-5 days, ICU mortality approximates 100% [37,66,83].

Acute respiratory failure in cancer patients admitted in the ICU

Data on the outcome of cancer patients admitted to the ICU for acute respiratory failure are limited, as most studies focus on patients in need of mechanical ventilation. One exception is the prospective study of Azoulay et al. [58], who used a clear definition of acute respiratory failure (respiratory rate > 30/min or respiratory distress symptoms, $PaO_2 < 60$ mm Hg at room air or need for ventilatory support) and reported an ICU mortality of 44.8% with hospital mortality of 47.3%. In that study, mortality was independently associated with the cause of acute respiratory failure: presence of cardiogenic pulmonary edema resulted to a better outcome and invasive aspergillosis to worse outcome. Other independent predictors of bad outcome were: a) no definite diagnosis (in many of these patients the presence of ARDS or fulminant disease did not allow thorough evaluation); b) vasopressors; c) first-line conventional mechanical ventilation; d) conventional mechanical ventilation after NIPPV failure; and e) late NIPPV failure (with very high ORs for the last three) [58].

In critically ill cancer patients, invasive mechanical ventilation seems to be the life-supporting treatment most closely associated with mortality [84]. According to the pooled results of 17 studies carried out between 1999 and 2005, and excluding recipients of HSCT, mortality was 81% for a total of 1456 patients in need of invasive MV (and only 50 % for a total of 348 patients in need of NIPPV) [84]. Delayed endotracheal intubation (after > 24 h at ICU) is associated with even worse outcome [30,59,62]. This was attributed to lack of response to initial ICU treatment and undeterred progression of acute respiratory failure [30,62].

In a recent study, Soares et al. studied the outcome of 463 mechanically ventilated cancer patients (96% of whom required invasive ventilation) [35]. Most patients (78%) had solid tumors, while BMT patients were excluded. Despite common co-existence of other acute organ failures, the ICU mortality in this cohort was 50% with a hospital mortality of 64%. Independent predictors for in-hospital mortality were age, performance status, recurrence/progression of cancer, $PaO_2/FiO_2 < 150$, SOFA excluding respiratory points, airway / pulmonary involvement by tumor as reason for MV.

Early initiation of NIPPV, wherever possible, can greatly improve the outcome of selected cancer patients with acute respiratory failure [36,41]. This benefit might be expected only if NIPPV is applied at an earlier, more compensated stage of respiratory failure [41,58]. The application of NIPPV or of invasive diagnostic modalities (like bronchoscopy) should not delay intubation and optimal management [58,84].

Interestingly, prolonging NIPPV for > 3 days has been associated with increased mortality compared to patients who improved earlier. This increase in mortality was the result of NIPPV failure and subsequent intubation (all of these patients died), while patients who despite long NIPPV avoided intubation finally had a good outcome [58]. It is unclear whether death in patients intubated after prolonged NIPPV was the result of a delay in optimal management with timely intubation, or of lung disease refractory to treatment in whom NIPPV simply postponed death, but who would have finally died even with early invasive MV.

Critically ill cancer patients with acute renal dysfunction

In critically ill patients with cancer, acute renal failure usually occurs in the context of multiple organ dysfunction and is associated with mortality ranging from 53 to 93% [6,34,54,62,85-89]. Most of these studies were restricted to patients receiving RRT.

Presence of a malignancy by itself is not a reason to withhold RRT in patients with acute renal failure, as short-term outcome depends not on the characteristics of cancer but on the number of organ failures at presentation and progression of organ failures [87-89]. On the other hand, non-adjusted hospital mortality was lower in patients who had RRT initiated on day 1 compared to patients who received RRT later; with RRT initiated after day 3, there were no survivors [89]. The appropriateness of the institution of RRT in patients who did not respond within 3-4 days of full ICU care should be discussed carefully [89].

Only one study provides data covering the whole spectrum of acute renal dysfunction in critically ill adult patients with cancer [89]. Soares et al. studied prospectively cancer patients (BMT excluded) with acute renal dysfunction (defined as serum creatinine > 1.44 mg/dl or oliguria) in the first 24 h from admission to the ICU. Acute renal dysfunction was present in 32% of admissions. Of these 54% had "injury" (serum creatinine 1.44 - 2.88 mg/dl), 25% "failure" (serum creatinine > 2.88 mg/dl) and 22% were in immediate need of RRT. Renal function worsened in 19% of patients during ICU stay and a further 10% had to be submitted to RRT. ICU, in-hospital and 6-month mortality was 55%, 64% and 73%, respectively. Independent predictors of bad outcome at 6 months were: a) age over 60; b) ECOG performance status 2-4; c) more than one associated organ dysfunctions; and d) presence of renal "failure" (instead of "injury"). More specifically, 6-month mortality was 38% with no or one risk factor, 84% with 2 or 3 risk factors, and 100% with 4 risk factors.

Sepsis / Septic shock

Sepsis is very common in patients with malignancy: a large epidemiological survey reports 995 cases of sepsis per 100000 cancer patients in 2001 [39]. Furthermore, in patients with sepsis, cancer is an independent predictor of death (adjusted OR 1,98) [39]. Interestingly, from 1979 to 2001 there has been a progressive decrease in the incidence of sepsis in cancer patients as well as a progressive decrease in mortality (from 44.7% to 23.8%). Similar trends have been observed in non-cancer patients [39].

In a recent study, cancer patients admitted to the ICU for septic shock had 30-day mortality 65.5% [37)]. In this study, independent predictors of mortality were only: a) time to antibiotic treatment >2 h; and b) progression of organ failures from day 1 to day 3 [37]. Neutropenia on admission does not seem to modify outcome [37,56]. Mortality is higher (87%) when septic shock occurs in cancer patients already admitted in the ICU [6] and in HSCT patients [27,32].

Hematopoietic stem cell transplantation

Critically ill patients with HSCT constitute a group with particularly high mortality [5,6,29,53,58,59,90-96]. Yet, when considering ICU admission in patients with HSCT, two facts should also be taken into account: a) prognosis may be grim for allogeneic BMT (which is associated with a higher risk of graft vs. host disease (GVHD) and higher intensity of immunosuppressive treatment), but is far better for autologous BMT [82] and for 'nonmyeloablative" stem cell transplantation [40]; b) patients with HSCT have potentially curable disease and many of those who survive till discharge from hospital remain alive at 6 months [97]. Furthermore, in part, probably because of better patient selection [98], there has been a steady improvement in the outcome of critically ill BMT patients over time [27,98]. Thus, Ferra et al. report a lower ICU mortality in 2004-2006 compared to 2000-2003 (49 vs. 69%) [98].

Respiratory failure that requires invasive mechanical ventilation is associated with very high mortality rates (85-90%) in patients with allogeneic BMT, particularly those receiving therapy for active severe GVHD or idiopathic pneumonia syndrome, while NIPPV is associated with better outcomes [15,27, 32,90-98].

A systematic review of the literature identified the following predictors of mortality in HSCT patients who require MV: a) prolonged MV (>3 days); b) FiO2 $\geq$ 0.6 at the commencement of the 2nd or 4th ICU day; c) more than 1 h of continuous vasopressor support within the first 3 days of ICU admission; d) simultaneously bilirubin > 4 mg/l and serum creatinine > 2 mg/dl upon admission, at 24 or 72 h; e) APACHE II score $\geq$29 on admission and at 24 h [97]. These predictors were validated in a prospective multicenter cohort of 226 patients with respiratory failure requiring MV within 1 year after allogeneic (71%) or autologous (29%) HSCT. Mortality rate in this cohort was 86%. It should be noted that no patient in this cohort survived the ICU

with: a) bilirubin > 4 mg/dl; and b) serum creatinine > 2 mg/dl upon admission, at 24 or 72 h [97].

Cancer chemotherapy in the ICU

For some patients admitted to the ICU with newly diagnosed untreated cancer, immediate cancer chemotherapy (first-line treatment) for acute, life-threatening cancer-related complications may be appropriate. Recent studies confirm that chemotherapy in this setting is feasible and may be beneficial in selected patients, while toxicities are manageable [99,100]. Independent predictors of 30-day mortality are need of vasopressors, MV and liver failure, while the coexistence of mechanical ventilation with hemodynamic instability portends a dismal outcome [99].

Acute life-threatening cancer-related events for which immediate chemotherapy may be indicated are bulky mediastinal disease with vascular or tracheobronchial compression, tumor lysis syndrome, leukostasis or pulmonary leukemic infiltration, spinal cord involvement, threatening malignancy-related diffuse intravascular coagulation (DIC), severe hemophagocytic syndrome in lymphomas, and hyperviscosity syndrome in multiple myeloma [3,29,99,100]. The question whether chemotherapy may also be delivered in the absence of an oncologic emergency or should always be deferred till exit from the ICU remains unanswered for the time being.

Cancer chemotherapy in the ICU is indicated mainly for hematologic malignancies, germ cell tumors and generally tumors with high chemosensitivity [99,100]. Limited data suggest that chemotherapy may also be beneficial in selected patients admitted to the ICU with newly diagnosed small cell lung cancer (SCLC) and favorable prognostic factors [101].

It should be noted that reports for immediate chemotherapy in critically ill cancer patients come from specialized ICUs, with close collaboration with hematologists and oncologists [99,100]. In a general ICU without specialized nursing staff, without oncologic consultation and with limited experience in the critically ill oncologic patient, this approach should probably be discouraged.

Finally, it should be stressed that use of chemotherapy to control the burden/spread of disease in critically ill patients with uncontrolled metastatic malignancy and progressive organ failure is unsupported by the medical literature and should be considered as unacceptable medical experimentation. In general, chemotherapy is also not recommended for patients with solid tumors or poor performance status. Such patients will experience greater toxicity, tolerate the treatment poorly and derive little, if any, benefit from chemotherapy [102,103].

Cardiopulmonary resuscitation of critically ill cancer patients

In the last few years, there is growing evidence to suggest that ICU management should be offered to selected groups of critically ill cancer patients [3]. Yet, cardiopulmonary resuscitation (CPR) of critically ill cancer patients should be viewed with great caution [104,105].

A meta-analysis of 42 studies with a total of 1707 adults patients with cancer who had in-hospital cardiopulmonary resuscitation reports a 6.2% survival to discharge [104], which is lower than the 15% rate of survival to discharge in unselected in-hospital cardiac arrests [106]. This data comes from a selected group with more favorable prognosis, as many patients with cancer have do-not-resuscitate (DNR) orders. Furthermore, the few data provided about post-resuscitation quality of life are sobering, and many of these cancer patients die shortly after discharge [104].

Survival is even lower (2.2%) when arrest occurs in the ICU [104]. A large retrospective study of 408 patients sheds further light on the outcome of cancer patients who underwent CPR in the ICU [105]. These patients represented a selected group of only 20% of cancer patients who had cardiopulmonary arrest - DNR orders were applied for the rest. From this group, 37% had spontaneous circulation restored and 28% survived more than 24 h, but only 2% were discharged from hospital. Survivors to discharge were only those patients who had acute ventricular dysrhythmias and were resuscitated promptly. These 7 patients had a reasonably good middle –term outcome. The authors rightly conclude that in cancer patients admitted to the ICU for full supportive care, cardiopulmonary resuscitation with chest compressions should be probably be discouraged.

Admission of critically ill cancer patients in the ICU – the ICU-trial policy

Although it is now clear that with appropriate selection critically ill cancer patients can survive the ICU, the decision to admit or refuse admittance to a particular patient is far from easy [71]. There is consensus that decision -making should be based on the following ethical principles: patient autonomy, benefi-

cence, non-maleficence and distributive justice [107]. If a therapeutic strategy has no hope of providing benefit to the patient but is likely to inflict pain, discomfort or loss of dignity, it must be regarded as harmful and should not be offered ("non-maleficence") [103]. Thus, there is agreement that cancer patients with proven uncontrollable or palliative disease (often defined as a life expectancy at 6 months of less than 1%) would usually not benefit from further ICU care [31,53,66]. The decision for admission needs also to integrate a reasonable probability of post-ICU quality of life, such as home discharge for a few months. Thus, patients' life expectancy without discomfort of ≥ 6 months has also been suggested for ICU admission [66]. Finally in patients with negative prognosis who do not respond to ICU treatment, one should be ready to discuss withholding / withdrawing treatment [108].

Decisions of admission should also take into account the burden of suffering in the ICU itself, which seems to be very high, even in ICUs who make special efforts to enhance patient comfort (experts in palliative medicine, liberal use of analgesics and sedatives, minimization of noise and night-time lightning) [109]. Since a high rate of distressing symptoms has been recorded in critically ill cancer patients, the preferences and values of patients and surrogates should be collected upstream from the ICU [110] and patients' autonomy should be respected [106]. A "shared" approach with the participation of the patient and/or family members in decision-making is desirable [107]. In practice, the final decisions are often influenced by the cultural milieu of both the patients' family and the ICU team [111,112].

Unluckily, as it has already been discussed, the ability to estimate at the time of ICU request probabilities of expected survival, is questionable [5,36,40, 49,53,67,71]. Even in specialised centers, criteria used to make triage decisions perform poorly [71]. On this aspect, the experience of Thiery et al. is very instructive [71]. They studied the outcome of patients with malignancies, for whom admission to the medical ICU was requested by ward physicians during a period of 1 year. Prerequisites for requesting admission were: a) presence of at least one-organ failure; b) patient's consent; c) availability of lifespan-extending treatment options for the malignancy. ICU admission was refused for about half of the referred cancer patients. 20% of patients who were not admitted because they were deemed too well to benefit from ICU management died before hospital discharge and 25% who were deemed too sick for ICU admission were discharged alive. Interestingly, 26% of the patients considered too sick to benefit, were still alive at 30 days, despite the fact that in most cases no lifespan-extending treatment options existed for the malignancy. Thus it seems that even when all hope for cancer control is lost the patient is not necessarily going to die in the short term, although questions still remain about the quality of life of these patients. Of the 47 patients considered too well to benefit, 13 were admitted to ICU later on, and had a 30-day mortality of 61.5% (compared with 6% for patients never admitted). Inappropriate delay in ICU admission cannot be ruled out as an explanation for the worse outcome. At 6 months, mortality was 61.8% for patients admitted to ICU, 83.3% for patients considered too sick to benefit from ICU admission and 42.2% for patients considered too well to benefit from ICU admission. The study of Thiery et al. offers strong arguments in support of ICU management rather than ICU refusal for cancer patients as it demonstrates that criteria for ICU admission are far from infallible while delayed admission is associated with high mortality rates [71].

In the last few years, the realization that the best predictor of survival for critically ill cancer patients is the evolution of organ failures during the patient's first 3 days in the ICU [27,37,53,66,67,82] has led to the development of a policy of ICU trial [3]. In this strategy, a trial of ICU therapy should be offered to all patients for whom a benefit from ICU management cannot be convincingly ruled out. Re-evaluation should follow to decide whether to continue full ICU treatment or switch to palliative care. In this way it is expected to eliminate: a) unwarranted refusals (associated with potential loss of chance); and b) unwarranted ICU management, responsible for unnecessary suffering of patients and family and for wasting of resources [3].

We provide a detailed description of the implementation of the ICU trial policy, as practiced by its proponents in St. Luis Hospital, Paris. Cancer patients with at least one organ failure, who are referred by the treating oncologist for ICU admission, are jointly evaluated by a senior intensivist and the ward oncologist in charge of the patient. The final decision is taken by a senior intensivist, who records the decision in the patients' chart as admission or refusal. In case of refusal, a second intensivist is involved in the decision [3,83].

In certain cases, ICU admission is refused out-of-hand and palliative care is recommended instead (Table 1). Some patients are also admitted without reservations, for full-code management, including unlimited life-sustaining interventions (Table 2) [3,83].

Between these two ends of the decision-making spectrum, decisions should be made on a case-by-case basis, based on clinical evaluation and after discussions with the oncologist and the patient. When uncertainty

Table 1. Reasons for refusing admittance to the ICU

Bedridden patients: patients who have spent most of their time at bed over the last 3 months preceding ICU admission and patients who have lost their ability to fully care for themselves
Non-availability of lifespan-extending treatment options for the malignancy
Patient refuses ICU admission

or disagreement exists, a trial of unlimited ICU management should be offered for a limited period, if patients and relatives are willing, to ensure that no patients are deprived of a chance for recovering from their acute complication. Then, the patient is re-evaluated taking into account both cancer and critical illness. After 3 days of full life-support management, a reduction in the number of organ failures indicates that additional life-sustaining treatment is the order. Absence of response or worsening, with no available therapeutic options, should prompt a discussion of the appropriateness of foregoing life-sustaining therapy. From day 5 onwards, treatment limitation decisions can be made after at least two staff meetings during which all intensivists, nurses and the haematologist/oncologist state their conviction that death would occur in the short term despite support for a new organ failure or maintenance of full life support. When family members are willing to participate in these decisions, they are encouraged to do so. Treatment limitation decisions are then recorded in detail in the patients' medical chart [3,83].

A recent prospective study demonstrated the feasibility of this strategy [83]. In this study, the best predictor of survival was logistic organ dysfunction score (LODS) on day 6. Dialysis, vasopressors or initiation of mechanical ventilation after day 3 of ICU stay indicated a very bad outcome (all patients died). Thus, in cancer patients with good performance status and lifespan-extending cancer therapy options, treatment decisions should not be made before day 6 of an ICU trial [83].

Finally, it should be stressed that proponents of a broad admission ICU policy are based on studies that are focused on relatively short-term survival. Questions on long - term outcome, quality of life or the emotional/financial burden remain for the time being unanswered. Only when information on all these questions become available will it be possible to formulate a rational policy for ICU admission of critically ill cancer patients.

Table 2. Indications of admission for full-code management, including unlimited life-sustaining interventions

Previously untreated malignancy
Acute tumor lysis syndrome
Bulky or infiltrating tumors at the earliest phase of treatment
Patients in complete remission

Conclusion

ICU management cannot be routinely considered futile in critically ill cancer patients. At the time of referral to the ICU, intensivists cannot discriminate between patients in whom ICU management may yield survival and quality of life benefits, and patients in whom the goal is a good death without the added suffering associated with ICU admission. Thus, in doubtful cases, use of liberal ICU admission criteria, with 3 to 6 days of full –code ICU management and further re-evaluation of the patient's status at this point is probably the best way to separate patients who may benefit from ICU management from those who should be transferred to palliative care.

References

1. Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. Lancet 2002; 360: 1131-1135.
2. Peters SG. Intensive care or end-of-life care for critically ill patients? Crit Care Med 2005; 33: 678-679.
3. Azoulay E, Afessa B. The intensive care support of patients with malignancy: do everything that can be done. Intensive Care Med 2006; 32: 3-5.
4. Task Force of the American College of Critical Care Medicine, Society of Intensive Care Medicine. Guidelines for intensive care admission discharge and triage. Crit Care Med 1999; 27: 633-638.
5. Kress JP, Christenson J, Pohlman AS, Linkin DR, Hall JB. Outcomes of critically ill cancer patients in a university hospital setting. Am J Respir Crit Care Med 1999; 160: 1957-1961.
6. Staudinger T, Stoiser B, Mullner M et al. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. Crit Care Med 2000; 28: 1322-1328.
7. Zarén B, Bergström R. Survival of intensive care patients. I: Prognostic factors from the patient's medical history. Acta Anaesthesiol Scand 1988; 32: 93-100.
8. Zarén B, Bergström R. Survival of intensive care patients. II: Outcome prediction 1 hour after admission. Acta Anaesthesiol Scand 1988; 32: 101-107.
9. Dragsted L, Qvist J. Outcome from intensive care. I. A 5-year study of 1308 patients: methodology and patient population. Eur J Anaesthesiol 1989; 6: 23-37.
10. Dragsted L, Qvist J, Madsen M. Outcome from intensive care. II. A 5-year study of 1308 patients: short-term outcome. Eur J Anaesthesiol 1989; 6: 131-144.

11. Kongsgaard UE, Meidell NK. Mechanical ventilation in critically ill cancer patients: outcome and utilisation of resources. Support Care Cancer 1999; 7: 95-99.
12. Niskanen M, Kari A, Halonen P. Five-year survival after intensive care-comparison of 12,180 patients with the general population. Finnish ICU Study Group. Crit Care Med 1996; 24: 1962-1967.
13. Schapira DV, Studnicki J, Bradham DD, Wolff P, Jarrett A. Intensive care survival and expense of treating critically ill cancer patients. JAMA 1993; 269: 783-796.
14. Lloyd-Thomas AR, Dhaliwal HS, Lister TA, Hinds CJ. Intensive therapy for life-threatening medical complications of haematological malignancy. Intensive Care Med 1986; 12: 317-324.
15. Crawford SW, Schwartz DA, Petersen FB, Clark JG. Mechanical ventilation after bone marrow transplantation. Risk factors and clinical outcome. Am Rev Respir Dis 1988; 137: 682-687.
16. Denardo SJ, Oye RK, Bellamy PE. Efficacy of intensive care for bone marrow transplant patients with respiratory failure. Crit Care Med 1989; 17: 4-6.
17. Snow RM, Miller WC, Rice DL, Ali MK. Respiratory failure in cancer patients. JAMA 1979; 241: 2039-2042.
18. Brunet F, Lanore JJ, Dhainaut JF et al. Is intensive care justified for patients with haematological malignancies? Intensive Care Med 1990; 16: 291-297.
19. Schuster DP, Marion JM. Precedents for meaningful recovery during treatment in a medical intensive care unit. Outcome in patients with hematologic malignancy. Am J Med 1983; 75: 402-408.
20. Butt W, Barker G, Walker C, Gillis J, Kilham H, Stevens M. Outcome of children with hematologic malignancy who are admitted to an intensive care unit. Crit Care Med 1988; 16: 761-764.
21. Faber-Langendoen K, Caplan AL, McGlave PB. Survival of adult bone marrow transplant patients receiving mechanical ventilation: a case for restricted use. Bone Marrow Transplant 1993; 12: 501-507.
22. Paz H, Crilley P, Weinar M, Brodsky I. Outcome of patients requiring medical ICU admission following bone marrow transplantation. Chest 1993; 104: 527-531.
23. Chaflin DB, Carlon GC. Age and utilization of intensive care unit resources of critically ill cancer patients. Crit Care Med 1990; 18: 694-698.
24. Sculier JP, Ries F, Verboven N, Coune A, Klastersky J. Role of intensive care unit in a medical oncology department. Eur J Cancer Clin Oncol 1988; 24: 513-517.
25. Sculier JP, Markiewicz E. Medical cancer patients and intensive care. Anticancer Res 1991; 11: 2171-2174.
26. Carlon GC. Admitting cancer patients to the intensive care unit. Crit Care Clin 1988; 4: 183-191.
27. Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: A case for evidence-based guidelines. Ann Intern Med 1996; 125: 625-633.
28. Sculier JP. Intensive care in the treatment of cancer patients. Curr Opin Oncol 1991; 3: 656-662.
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: 1395-1401.
30. Groeger JS, White P Jr, Nierman DM et al. Outcome for cancer patients requiring mechanical ventilation. J Clin Oncol 1999; 17: 991-997.
31. Sculier JP, Paesmans M, Markiewicz E, Berghmans T. Scoring systems in cancer patients admitted for an acute complication in a medical intensive care unit. Crit Care Med 2000; 28: 2786-2792.
32. 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: 1715-1721.
33. Kroschinsky F, Weise M, Illmer T et al. Outcome and prognostic features of intensive care unit treatment in patients with hematological malignancies. Intensive Care Med 2002; 28: 1294-1300.
34. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognostic indicators in patients with hematologic malignancy admitted to the intensive care for a life-threatening complication. Crit Care Med 2003; 31: 104-112.
35. Soares M, Salluh JI, Spector N, Rocco JR. Characteristics and outcomes of cancer patients requiring mechanical ventilation support for more than 24 hours. Crit Care Med 2005; 33: 520-526.
36. Azoulay E, Alberti C, Bornstain C et al. Improved survival in cancer patients requiring mechanical ventilatory support: impact of non-invasive mechanical ventilatory support. Crit Care Med 2001; 29: 519-525.
37. Larche J, Azoulay E, Fieux F et al. Improved survival of critically ill cancer patients with septic shock. Intensive Care Med 2003; 29: 1688-1695.
38. Moran JL, Solomon PJ, Williams PJ. Assessment of outcome over a 10-year period of patients admitted to a multidisciplinary adult intensive care unit with haematological and solid tumours. Anaesth Intensive Care 2005; 33: 26-35.
39. Danai PA, Moss M, Mannino DM, Martin GS. The epidemiology of sepsis in patients with malignancy. Chest 2006; 129: 1432-1440.
40. Khassawneh BY, White P Jr, Anaissie EJ, Barlogie B, Hiller FC. Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. Chest 2002; 121: 185-188.
41. Hilbert G, Gruson D, Vargas F et al. Non-invasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001; 344: 481-487.
42. Afessa B, Tefferi A, Litzow MR, Peters SG. Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med 2002; 166: 1364-1368.
43. Azoulay E, Fieux F, Moreau D et al. Acute monocytic leukemia presenting as acute respiratory failure. Am J Respir Crit Care Med 2003; 167: 1329-1333.
44. Wössmann W, Schrappe M, Meyer U, Zimmermann M, Reiter A. Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. Ann Hematol 2003; 82: 160-165.
45. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342: 1301-1308.
46. Rivers E, Nguyen B, Havstad S et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345: 1368-1377.

47. Azoulay E, Pochard F, Chevret S et al. PROTOCETIC Group. Compliance with triage to intensive care recommendations. Crit Care Med 2001; 29: 2132-2136.
48. Garrouste-Orgeas M, Montuclard L, Timsit JF et al. French ADMISSIONREA Study Group. Predictors of intensive care unit refusal in French intensive care units: a multiple-center study. Crit Care Med 2005; 33: 750-755.
49. Azoulay E, Moreau D, Alberti C et al. Predictors of short-term mortality in critically ill patients with solid malignancies. Intensive Care Med 2000; 26: 1817-1823.
50. Abbas FM, Sert MB, Rosenshein NB, Zahyrak ML, Currie JL. Gynecologic oncology patients in the surgical ICU. Impact on outcome. J Reprod Med 1997; 42: 173-178.
51. Leath CA 3rd, Kendrick JE 4th, Numnum TM et al. Outcomes of gynecologic oncology patients admitted to the intensive care unit following surgery: A university teaching hospital experience. Int J Gynecol Cancer 2006; 16: 1766-1769.
52. Blot F, Guiguet M, Nitenberg G, Leclerq 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: 1031-1037.
53. Massion PB, Dive AM, Bulpa P, Jamart J, Bolsy A, Installe E. Prognosis of hematologic malignancies does not predict intensive care unit mortality. Crit Care Med 2002; 30: 2260-2270.
54. Darmon M, Azoulay E, Alberti C et al. Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients. Intensive Care Med 2002; 28: 1775-1780.
55. Vallot F, Paesmans M, Berghmans T, Sculier JP. Leucopenia is an independent predictor in cancer patients requiring invasive mechanical ventilation: a prognostic factor analysis in a series of 168 patients. Support Care Cancer 2003; 11: 236-241.
56. Regazzoni CJ, Irrazabal C, Luna CM, Poderoso JJ. Cancer patients with septic shock: mortality predictors and neutropenia. Support Care Cancer 2004; 12: 833-839.
57. Epner DE, White P, Krasnoff M, Khanduja S, Kimball KT, Knaus WA. Outcome of mechanical ventilation for adults with hematologic malignancy. J Investig Med 1996; 44: 254-260.
58. Azoulay E, Thiery G, Chevret S et al. The prognosis of acute respiratory failure in critically ill cancer patients. Medicine 2004; 83: 360-370.
59. Depuydt PO, Benoit DD, Vandewoude KH, Decruyenaere JM, Colardyn FA. Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. Chest 2004; 126: 1299-1330.
60. Boussat S, Elrini T, Dubiez A, Depierre A, Barale F, Capellier G. Predictive factors of death in primary lung cancer patients on admission to the intensive care unit. Intensive Care Med 2000; 26: 1811-1816.
61. Rabbat A, Chaoui D, Montani D et al. Prognosis of patients with acute myeloid leukaemia admitted to intensive care. Br J Haematol 2005; 129: 350-357.
62. 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: 761-770.
63. Soares M, Carvalho MS, Salluh JI et al. Effect of age on survival of critically ill patients with cancer. Crit Care Med 2006; 34: 912-923.
64. Soares M, Salluh JI, Toscano L, Dias FL. Outcomes and prognostic factors in patients with head and neck cancer and severe acute illnesses. Intensive Care Med 2007; 33: 2009-2013.
65. Christodoulou C, Rizos M, Galani E, Rellos K, Skarlos DV, Michalopoulos A. Performance status (PS): a simple predictor of short-term outcome of cancer patients with solid tumors admitted to the intensive care unit (ICU). Anticancer Res 2007; 27: 2945-2948.
66. Guiguet M, Blot F, Escudier B, Antoun S, Leclercq B, Nitenberg G. Severity-of-illness scores for neutropenic cancer patients in an intensive care unit: Which is the best predictor? Do multiple assessment times improve the predictive value? Crit Care Med 1998; 26: 488-493.
67. Blot F, Cordonnier C, Buzin A, Nitenberg G, Schlemmer B, Bastuji-Garin S. Club sur L'Infection en Onco-Hematologie. Severity of illness scores: are they useful in febrile neutropenic adult patients in hematology wards? A prospective multicenter study. Crit Care Med 2001; 29: 2125-2131.
68. Headley J, Theriault R, Smith TL. Independent validation of APACHE II severity of illness score for predicting mortality in patients with breast cancer admitted to the intensive care unit. Cancer 1992; 70: 497-503.
69. Van Le L, Fakhry S, Walton LA, Moore DH, Fowler WC, Rudledge R. Use of the APACHE II scoring system to determine mortality of gynecologic oncology patients in the intensive care. Obstet Gynecol 1995; 85: 53-56.
70. Soares M, Salluh JI. Validation of the SAPS 3 admission prognostic model in patients with cancer in need of intensive care. Intensive Care Med 2006; 32: 1839-1844.
71. 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: 4406-4413.
72. den Boer S, de Keizer NF, de Jonge E. Performance of prognostic models in critically ill cancer patients-a review. Crit Care 2005; 9: R458-463.
73. Soares M, Fontes F, Dantas J et al. Performance of six -of-illness scores in cancer patients requiring admission to the intensive care unit: a prospective observational study. Crit Care 2004; 8: R194-R203.
74. Groeger JS, Glassman J, Nierman DM et al. Probability of mortality of critically ill cancer patients at 72 h of intensive care unit (ICU) management. Support Care Cancer 2003; 11: 686-695.
75. Berghmans T, Paesmans M, Sculier JP. Is a specific oncological scoring system better at predicting the prognosis of cancer patients admitted for an acute medical complication in an intensive care unit than general gravity scores? Support Care Cancer 2004; 12: 234-239.
76. Schellongowski P, Benesch M, Lang T et al. Comparison of three severity scores for critically ill cancer patients. Intensive Care Med 2004; 30: 430-436.
77. Cornet AD, Issa AI, van de Loosdrecht AA et al. Sequential organ failure predicts mortality of patients with a haematological malignancy needing intensive care. Eur J Haematol 2005; 74: 511-516.
78. Soares M, Darmon M, Salluh JI et al. Prognosis of lung cancer patients with life-threatening complications. Chest 2007; 131: 840-846.
79. Timsit JF, Fosse JP, Troche G et al. Accuracy of a composite score using daily SAPS II and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 h. Intensive Care Med 2001; 27: 1012-1021.
80. Afessa B, Keegan MT, Mohammad Z, Finkielman JD, Peters SG. Identifying potentially ineffective care in the sickest critically ill patients on the third ICU day. Chest 2004; 126: 1905-1909.

81. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluations of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286: 1754-1758.
82. Pène 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: 643-649.
83. Lecuyer L, Chiery 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: 808-814.
84. Azoulay E, Schlemmer B. Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 2006; 32: 808-822.
85. Lanore JJ, Brunet F, Pochard F et al. Hemodialysis for acute renal failure in patients with hematologic malignancies. Crit Care Med 1991; 19: 346-351.
86. Berghmans T, Meert AP, Markiewicz E, Sculier JP. Continuous venovenous haemofiltration in cancer patients with renal failure: a single-centre experience. Support Care Cancer 2004; 12: 306-311.
87. Benoit DD, Hoste EA, Depuydt PO et al. Outcome in critically ill medical patients treated with renal replacement therapy for acute renal failure: comparison between patients with and those without haematological malignancies. Nephrol Dial Transplant 2005; 20: 552-558.
88. 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: 765-772.
89. Soares M, Salluh JI, Carvalho MS, Darmon M, Rocco JR, Spector N. Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol 2006; 24: 4003-4010.
90. Torrecilla C, Cortes JL, Chamorro C, Rubio JJ, Galdos P, Dominguez de Villota E. Prognostic assessment of the acute complications of bone marrow transplantation requiring intensive therapy. Intensive Care Med 1988; 14: 393-398.
91. Crawford SW, Petersen FB. Long-term survival from respiratory failure after marrow transplantation for malignancy. Am Rev Respir Dis 1992; 145: 510-514.
92. Hollmig KA, Soehngen D, Leschke M et al. Long-term survival of recipients of allogenic bone-marrow transplantation after mechanical ventilation. Eur J Med Res 1997; 2: 62-66.
93. Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW. Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. Transplantation 1997; 63: 1079-1086.
94. Shorr AF, Moores LK, Edenfield WJ, Christie RJ, Fiitzpatrick TM. Mechanical ventilation in hematopoietic stem cell transplantation: can we effectively predict outcomes? Chest 1999; 116: 1012-1018.
95. Huaringa AJ, Leyva FJ, Giralt SA et al. Outcome of bone marrow transplantation patients requiring mechanical ventilation. Crit Care Med 2000; 28: 1014-1017.
96. Soubani AO, Kseibi E, Bander JJ et al. Outcome and prognostic factors of hematopoietic stem cell transplantation recipients admitted to a medical ICU. Chest 2004; 126: 1604-1611.
97. Bach PB, Schrag D, Nierman DM et al. Identification of poor prognostic features among patients requiring mechanical ventilation after hematopoietic stem cell transplantation. Blood 2001; 98: 3234-3240.
98. Ferra C, Marcos P, Misis M et al. Outcome and prognostic factors in patients with hematologic malignancies admitted to the intensive care unit: a single-center experience. Int J Hematol 2007; 85: 195-202.
99. Darmon M, Thiery G, Giroldi M et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. Crit Care Med 2005; 33: 2488-2493.
100. 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: 93-99.
101. Jennens RR, Rosenthal MA, Mitchell P, Presneill JJ. Outcome of patients admitted to the intensive care unit with newly diagnosed small cell lung cancer. Lung Cancer 2002; 38: 291-296.
102. Tanvetyanon T. Consideration before administering cytotoxic chemotherapy to the critically ill. Crit Care Med 2005; 33: 2689-2691.
103. Marik PE. Management of patients with metastatic malignancy in the intensive care unit. Am J Hospice and Palliative Medicine 2007; 23: 479-482.
104. Reisfield GM, Wallace SK, Munsell MF, Webb FJ, Alvarez ER, Wilson GR. Survival in cancer patients undergoing in-hospital cardiopulmonary resuscitation: a meta-analysis. Resuscitation 2006; 71: 152-160.
105. Wallace SK, Ewer MS, Price KJ, Feeley TW. Outcome and cost implications of cardiopulmonary resuscitation in the medical intensive care unit of a comprehensive cancer center. Support Cancer Care 2002; 10: 425-429.
106. Saklayen M, Liss H, Markert R. In-hospital cardiopulmonary resuscitation. Survival in 1 hospital and literature review. Medicine 1995; 74: 163-175.
107. Carlet J, Thijs LG, Antonelli M et al. Challenges in end-of-life care in the ICU. Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003. Intensive Care Med 2004; 30: 770-784.
108. Withholding and withdrawing life-sustaining therapy. Official Statement of the American Thoracic Society. Am Rev Respir Dis 1991; 144: 726-731.
109. Nelson JE, Meier DE, Oei EJ et al. Self-reported symptom experience of critically ill patients receiving intensive care. Crit Care Med 2001; 29: 277-282.
110. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002; 346: 1061-1066.
111. Sprung CL, Cohen SL, Sjokvist P et al. Ethicus Study Group. End-of-life practices in European intensive care units: the Ethicus Study. JAMA 2003; 290: 790-797.
112. Sprung CL, Woodcock T, Sjokvist P et al. Reasons, considerations, difficulties and documentation of end-of-life decisions in European intensive care units: the ETHICUS Study. Intensive Care Med 2007 Nov 9; [Epub ahead of print].