ARTICLE TITLE: Critical Care of Patients With Cancer

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EDUCATIONAL OBJECTIVES:
After reading the article “Critical Care of Patients With Cancer,” the learner should be able to:
1. Describe the evolution of critical care for patients with cancer.
2. Relate key principles of intensive care for critically ill patients with cancer.
3. Discuss the referral and management of critically ill patients with cancer in the intensive care unit.
4. Define the long-term impact of intensive care treatment on patients with cancer, their relatives, and caregivers.

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Critical Care of Patients With Cancer

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ABSTRACT: The increasing prevalence of patients living with cancer in conjunction with the rapid progress in cancer therapy will lead to a growing number of patients with cancer who will require intensive care treatment. Fortunately, the development of more effective oncologic therapies, advances in critical care, and improvements in patient selection have led to an increased survival of critically ill patients with cancer. As a consequence, critical care has become an important cornerstone in the continuum of modern cancer care. Although, in many aspects, critical care for patients with cancer does not differ from intensive care for other seriously ill patients, there are several challenging issues that are unique to this patient population and require special knowledge and skills. The optimal management of critically ill patients with cancer necessitates expertise in oncology, critical care, and palliative medicine. Cancer specialists therefore have to be familiar with key principles of intensive care for critically ill patients with cancer. This review provides an overview of the state-of-the-art in the individualized management of critically ill patients with cancer. CA Cancer J Clin 2016;66:496–517. © 2016 American Cancer Society.

Keywords: cancer, critical care, oncology, palliative care

Practical Implications for Continuing Education

> The prognosis of critically ill patients with cancer has improved over recent decades.

> Optimal care for critically ill patients with cancer requires specialized knowledge and multidisciplinary management.

> Characteristics of the underlying malignancy such as tumor entity, disease stage, or remission status have little impact on short-term survival after ICU admission.

Introduction

Cancer is a major public health problem worldwide.1 In many developed countries, it is expected that cancer will soon become the leading cause of death.2 Progress in cancer treatment results in a growing number of patients who are not cured but live with cancer. Because the number of patients living with cancer will increase, it can be expected that there will also be more patients with cancer who require intensive care treatment.

Patients with cancer are a particularly vulnerable patient population. Cancer often is still regarded as a fatal disease for which intensive care unit (ICU) admission is not justified, although many types of cancer can be cured or managed as chronic diseases, and many nonmalignant diseases carry an equally poor prognosis as some of the worst types of cancer.3 The special nature of the cancer diagnosis and the resulting implications for their management set apart patients who have cancer from other critically ill patients in the ICU. The unique status and medical problems of critically ill patients with cancer underscore the need for a special approach to this patient population. This review is intended to equip oncologists and
hematologists with a framework for the delivery of high-value care for critically ill patients with malignancies.

Evolution of Critical Care for Patients With Cancer

The number of hospitalized patients who receive intensive care treatment is growing. Since its beginnings in the 1950s, the field of critical care has made major advances. Improvements in critical care have come from several different developments. Technological innovations like the invention of advanced organ support systems, including renal dialysis and extracorporeal membrane oxygenation, currently enable the temporary replacement of critical organ functions. In addition to technological advances, the major drivers of progress in intensive care medicine have been findings from basic research, which have led to a better understanding of the pathophysiology of conditions affecting critically ill patients, and the results from clinical trials. Insights from randomized controlled studies have facilitated the evidence-based management of critically ill patients and have led to incremental improvements in patient outcome.

Recent statistics demonstrate that the survival of patients with cancer is improving. Reasons include better screening and early detection, more specific and effective treatments, as well as improvements in the management of side effects. In recent years, the treatment of cancer has undergone a paradigm change. The concept of precision medicine has dramatically changed the management of many cancers. A constantly growing, expanding armamentarium of more specific and effective anticancer agents offers oncologists a remarkable variety of options from which to choose. The combination of these agents into novel treatment regimens promises further improvements in the efficacy of cancer therapy. These advances foretell a future in which a functional cure for some malignancies is possible and cancer is transformed into a chronic but manageable disease.

Approximately 5% to 10% of patients with cancer will develop a life-threatening condition that necessitates ICU admission. In a study conducted in France, admission rates for patients with differing cancer entities varied between 0.7% and 12%. Patients with certain malignant diseases, such as esophageal cancer or acute leukemia, and those undergoing allogeneic stem cell transplantation have particularly high ICU utilization rates of up to almost 30%. Currently, patients with malignancies account for approximately 13.5% to 21.5% of all ICU admissions. In the past, patients with cancer, especially those with solid tumors, were frequently denied access to the ICU. However, recent progress in cancer therapy and intensive care has improved the prognosis of critically ill patients with cancer. A growing number of studies demonstrate that seriously ill patients with cancer can benefit from intensive care treatment.

Many case reports or small case series describing successful critical care treatment of patients with malignancies illustrate how multidisciplinary management that makes use of the full spectrum of modern intensive care and experimental therapeutic approaches can be a lifesaving strategy in selected patients with cancer who are critically ill. Although many problems that are encountered in critically ill patients with cancer also apply to patients without cancer, this patient population has specific characteristics and needs. Critically ill patients with cancer can present with a variety of cancer-specific complications and conditions, such as leukostasis, superior vena cava syndrome, or paraneoplastic autoimmune phenomena. The appropriate management of these conditions demands profound knowledge in oncology that is beyond the scope of most intensive care specialists.

The current literature shows a steady trend toward improved outcomes of patients with hematologic or solid cancers who require critical care management (Fig. 1). Until the turn of the century, reported survival rates for critically ill patients with cancer were in the range from 20% to 30%. More recently, reported ICU survival rates for critically ill patients with cancer have increased to around 50% to 60%. A French retrospective cohort study of prospectively collected data from 3437 critically ill patients with cancer demonstrated a continuous drop in ICU mortality from 70.4% to 52.5% over the 12-year period from 1997 to 2008. Although ICU patients with cancer still have a higher mortality than ICU patients without malignancy, published survival rates of critically ill patients with cancer are approaching those of severely ill patients without cancer, and it no longer seems justified to universally deny patients with cancer access to intensive care medicine.

However, caution is needed when interpreting the results in the literature on ICU treatment for patients with cancer and when deriving conclusions for clinical practice. The vast majority of studies is retrospective and demonstrates considerable heterogeneity. It remains controversial whether the observed improvements in survival of critically ill patients with cancer can be solely the result of advances in treatment of the underlying malignancy and progress in critical care. Part of the improvements that were seen could be because of selection bias or earlier ICU admission of critically ill patients with cancer. Furthermore, there are substantial practice variations at the physician, hospital, country, and temporal levels. Thus, published data concerning cancer critical care, such as changes in ICU survival of patients with cancer, may be confounded by differences in clinical practice, case mix, and admission policies.
Interdisciplinary Care for Critically Ill Patients With Cancer

Optimal care for patients with cancer requires detailed knowledge of the typical serious disease-related and treatment-related complications that occur in this patient population and their appropriate medical management. Keeping up with the latest developments in cancer therapeutics as well as their adverse effects and drug interactions has become increasingly difficult, because the number of anticancer agents and their associated side-effect profiles are growing at a rapid pace. Because of the complexity of their conditions, care for critically ill patients with cancer requires interdisciplinary medical management. Clinical evidence documents that the establishment of multidisciplinary care teams has contributed to lowering ICU mortality. Therefore, care for unstable patients with cancer should best be provided by an interdisciplinary team providing expertise in critical care, oncology, and palliative care.

The patient’s oncologic team plays a central role in the management of a critically ill patient with cancer. Physician members of the oncology care team are in an ideal position for the early identification of deteriorating patients with cancer who may require more aggressive medical therapy. Apart from guiding oncologic treatment, oncologists/hematologists are important partners for the intensive care team who can contribute to the optimal management of critically ill patients with cancer by providing advice with regard to the oncologic aspects of the patient’s care.

Many hospitals today have introduced rapid response teams. These teams consist of a designated group of critical care physicians and/or critical care nurses who can assist the oncologist in charge in deciding which patients are likely to benefit from transfer to ICU for more intense medical therapy. The creation of rapid response teams is one promising approach to identifying critically ill patients with cancer who are at imminent risk of further deterioration before serious irreversible organ failure has occurred. In a retrospective observational study investigating the role of early activation of a rapid response team, in-hospital mortality was 32% after early intervention versus 73% after late intervention. Moreover, the results of a small prospective observational study suggest that assistance by a rapid response team can improve the management of critically ill patients with cancer who stay on the ward. That study analyzed 77 critically ill patients with cancer who were managed on the ward and demonstrated that patients who were managed jointly with a rapid response team had a survival rate of 68% compared with 60% for those who were treated by the primary oncologic team only. An additional benefit of rapid response teams could be that they can initiate discussions about appropriate treatment goals and thus reduce inappropriate ICU admissions.

Unfortunately, there are still substantial organizational and cultural barriers that prevent more effective multidisciplinary care for critically ill patients with cancer. The degree of interdisciplinarity necessary for the care of this patient population can also serve as a source of conflict and requires a mutual understanding of differences in perspective. Oncologists often take on an overly

FIGURE 1. Improvement in Survival of Critically Ill Patients With Cancer During the Last Decades. (a) Intensive care unit (ICU) survival, (b) hospital survival, and (c) 1-year survival are illustrated. The results shown are from publications that reported the survival of critically ill patients with cancer who required ICU admission. Each color represents the mean survival reported in one study, and the color of the dots represents the patient population. Green denotes studies that reported the survival of patients with hematologic malignancies (HM), blue denotes studies that reported the survival of patients with solid tumors (ST), and red denotes studies that reported the survival of mixed patient populations, which included patients with HM and those with ST.
optimistic viewpoint. They often do not provide a frank estimate of prognosis to the patient and tend to overestimate the effectiveness of cancer therapy. This seems particularly true for novel targeted therapies even when little is known about how well novel treatment modalities work in critically ill patients with cancer. The limited data that have been published indicate that even novel and more effective anticancer agents often do not improve the outcome of patients with cancer in the ICU.

Intensivists, conversely, may oppose ICU admission of patients with cancer because of insufficient knowledge about the prognosis and treatment of this patient population. Studies among intensive care specialists have shown that a diagnosis of malignancy is associated with an almost 6-fold increased likelihood of refusal of ICU admission or limitation of aggressive treatment.

Palliative care is a core component of excellent cancer care. It has been shown that the introduction of palliative care services early after a diagnosis of cancer improves quality of life and reduces the use of aggressive end-of-life care. Apart from helping to limit unnecessary ICU admission and aggressive therapy in the last weeks of life, palliative care medicine can also play an important role during ICU treatment. The integration of palliative medicine into critical care can improve the ICU experience of patients and their families and can furthermore ease the transition from a curative intent to forgoing life-sustaining treatment. Therefore, palliative care should be offered parallel to life-sustaining therapy.

### ICU Referral of Critically Ill Patients With Cancer

#### Indications for ICU Admission of Patients With Cancer

Patients with cancer may require intensive medical therapy for a broad range of indications. In most cases, the need for intensive care treatment either is because of the malignancy itself or is a consequence of complications of cancer therapy. Table 1 summarizes the most frequent indications for which patients with cancer might require intensive care support. Contingent upon the type of ICU and the corresponding medical institution, the relative proportions of ICU admissions for medical or postsurgical care can vary. In general, when admissions for postoperative care are excluded, patients with hematologic malignancies are more frequently transferred to the ICU than patients with solid tumors.

Some patients with cancer require critical care for an early complication of their malignancy. Examples for early manifestations of cancer that can lead to the need for ICU admission include hypercalcemia, tumor lysis syndrome, superior vena cava syndrome, or pulmonary embolism.

Other frequent indications for ICU admission are the result of complications of cancer therapy. The most common treatment-related indications for ICU admission in patients with cancer are caused by infection as a consequence of chemotherapy-induced neutropenia. Despite improvements in the prevention and management of nosocomial infections, patients with cancer are at a higher risk of developing severe sepsis than patients without cancer, and almost every 10th patient with cancer dies of sepsis.

The risk of developing severe sepsis is almost 9 times higher for patients with hematologic malignancies than for

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**TABLE 1. Causes for Intensive Care Unit Admission of Patients With Cancer**

| Infections          |          |
|---------------------|----------|
| Pneumonia           |          |
| Sepsis              |          |
| Oncologic emergencies |        |
| Superior vena cava syndrome | |
| Tumor lysis syndrome |          |
| Hypercalcemia       |          |
| Noninfectious ARF   |          |
| TRALI               |          |
| TACO                |          |
| Pneumonitis         |          |
| Alveolar hemorrhage |          |
| Engraftment syndrome|          |
| Surgery             |          |
| Regular postsurgical care | |
| Postsurgical complications, eg, bleeding | |
| Adverse drug reactions |       |
| Anaphylaxis         |          |
| Cytokine release syndrome | |
| ATRA syndrome       |          |
| Thrombotic microangiopathy | |
| Neurologic complications |   |
| Seizures            |          |
| PRES                |          |
| Cardiovascular disease |      |
| Myocardial infarction |        |
| Congestive heart failure |    |
| Arrhythmias         |          |
| Pulmonary thromboembolism |  |

ARF indicates acute respiratory failure; ATRA, all-trans retinoic acid; ICU, intensive care unit; PRES, posterior reversible encephalopathy syndrome; TRALI, transfusion-associated lung injury; TACO, transfusion-associated circulatory overload. The list summarizes some of the most frequent causes for ICU admission of patients with cancer.
patients with solid tumors and is 15 times higher than for the general population.\textsuperscript{65} Other examples of therapy-induced complications include anaphylaxis, cytokine release syndrome, or drug-induced organ failure.

Acute respiratory failure is the most frequent medical reason for ICU referral of patients with cancer.\textsuperscript{66,67} The risk of acute respiratory failure is higher in patients with hematologic malignancies than in patients with solid tumors. In particular, neutropenic patients and patients undergoing allogeneic stem cell transplantation are at a very high risk of developing acute respiratory failure.\textsuperscript{13,68} The most common etiologies of acute respiratory failure in patients with cancer are primary infections, which account for approximately 65\% of all cases of acute respiratory distress syndrome in patients with cancer.\textsuperscript{69} Neutropenic patients with cancer can develop a distinct form of acute respiratory distress syndrome that occurs during the phase of recovery from neutropenia in association with preexistent pneumonia and administration of granulocyte-colony-stimulating factor (G-CSF).\textsuperscript{70-74} Other frequent causes of acute respiratory failure include treatment-associated respiratory toxicities, pulmonary comorbidities, lung involvement by the underlying malignancy, cardiogenic pulmonary edema, diffuse alveolar hemorrhage, noninfectious pneumonia, and transfusion-associated acute lung injury. In patients with acute leukemia, respiratory failure can be caused by leukemic infiltration, leukostasis, or acute lysis pneumopathy.\textsuperscript{75}

Acute kidney failure occurs in 12\% to 36\% of patients with cancer and is accompanied by substantial morbidity and mortality.\textsuperscript{76-78} From 16\% to 23\% of patients with cancer who are admitted to the ICU develop severe renal failure and require renal replacement therapy.\textsuperscript{79,80} The etiology of renal failure in patients with cancer is often multifactorial and can be caused by the tumor itself or by drug-related toxicity.\textsuperscript{81-83} Among the most frequent causes of renal failure in patients with cancer are toxicity of chemotherapy and tumor lysis syndrome. Patients with hematologic malignancies are at a higher risk of developing acute renal failure than patients with solid tumors.\textsuperscript{84}

Neurological symptoms, such as confusion, coma, or seizures, are another frequent indication for ICU admission. Central nervous system complications can be caused by malignant infiltration of the brain, intracranial hemorrhage, treatment-related toxicity, posterior reversible encephalopathy syndrome, or infection.\textsuperscript{85,86}

Occasionally, ICU admission is requested for patients who have advanced cancer and no curative treatment options. Although an aggressive treatment approach cannot be recommended for this patient group, short-term ICU admission may be appropriate for the management of reversible conditions, such as cardiac tamponade or respiratory insufficiency, which can be managed with noninvasive ventilation (NIV). Very rarely, palliative patients with cancer without further treatment options are admitted to the ICU for symptom management that cannot easily be provided elsewhere, such as palliative sedation for intractable pain.

Prognosis of Critically Ill Patients With Cancer

The reported mortality rates for patients with cancer who are treated in the ICU vary widely. These variations are indicative of the difficulty of prognostication in critically ill patients with cancer and partly reflect various admission criteria for these patients. Clinical studies have distinguished several prognostic factors that identify patients with cancer who have high ICU mortality and can help in triaging patients for ICU admission.

In most studies, patients with hematologic malignancies have a worse ICU survival than patients with solid tumors.\textsuperscript{87} The causes of this discrepancy are multifactorial and include differences in selection criteria, comorbidities, and indications for admission. Surprisingly, apart from these differences, characteristics of the underlying malignancy, such as tumor entity, disease stage, or remission status, have a negligible impact on short-term survival after ICU admission and only affect the long-term prognosis.\textsuperscript{88-90}

The cause of ICU admission affects the prognosis of patients with cancer. Patients with solid tumors are frequently admitted to the ICU for routine postoperative care after undergoing definitive surgical treatment of their underlying malignancy. In an analysis of the Dutch National Intensive Care Evaluation Registry, patients who were admitted after elective cancer surgery accounted for 9\% of all ICU admissions. Those patients generally have a good prognosis with low hospital mortality.\textsuperscript{91-96} Even patients who need to be readmitted to the ICU because of complications related to surgery have a satisfactory outcome.\textsuperscript{16,97,98} Conversely, patients who are admitted to the ICU for medical reasons have a worse outcome than surgical patients with cancer.\textsuperscript{15,99} A prospective, multicenter, cohort study in 28 Brazilian ICUs found that patients who were admitted for medical reasons had an in-hospital mortality rate of 58\% compared with 37\% and 11\% for patients who were admitted after emergency surgery or scheduled surgery, respectively.\textsuperscript{15} In that study, the median length of stay in the ICU was 2 days, and the ICU mortality rate was 6\% for patients who were admitted after elective surgery compared with a median length of stay of 5 days and an ICU mortality rate of 23\% for patients after emergency surgery.\textsuperscript{15}

As a consequence of improvements in critical care, several prognostic factors that were previously considered important predictors of a poor outcome have become less relevant. For instance, neutropenia has long been a major negative prognostic factor; but, with the increasing
availability of better antimicrobial agents and G-CSF, the
significance of neutropenia for the prognosis of patients has
decreased.100-103 Notably, ICU admission because of bacte-
rrial infections is associated with a better prognosis than
most other complications that lead to ICU referral.104-106

A history of autologous stem cell transplantation was
previously associated with a poor prognosis in critically ill
patients with cancer; however, with advances in supportive
therapy, their outcomes have improved. Before the year
2000, the reported ICU survival rates for patients after
autologous stem cell transplantation were below 30%.107,108
Since then, the survival of critically ill patients who have
undergone autologous transplantation has improved sub-
stantially.109-111 Therefore, currently, autologous stem cell
transplantation can no longer be viewed as an adverse prog-
nostic factor that negatively affects the trajectory of crit-
ically ill patients with cancer.

Despite advances in intensive care management, there are
several negative predictive factors that have remained rela-
tant. Age and poor performance status have maintained their
negative prognostic value.15,112 Multiorgan failure is a major
prognostic factor for patient outcome.102,113 Increasing num-
bers of organ failures are associated with a corresponding
decrease in survival, and high sequential organ failure assess-
ment (SOFA) scores are predictive of a poor outcome.114
The type and number of organ failures and their develop-
ment over time are among the most important determinants
of the patient’s disease trajectory during the ICU stay.115,116

Acute respiratory failure is a leading cause of ICU admis-
sion and often results in mechanical ventilation of the
patient. Mechanical ventilation, especially when prolonged,
is a major negative prognostic factor and is associated with
significantly increased mortality.102,104,117-119 The survival
of patients who require mechanical ventilation has improved
in the last 2 decades but still remains poor (Fig. 2).

Likewise, acute renal failure is predictive of a poor out-
come especially if dialysis is required.82,117,120-122 Even
small increases in creatinine correlate with increased mor-
bidity and mortality.76,123 Acute kidney injury in patients
with cancer has been associated with a 3-day longer hospita-
al stay, $42,671 higher hospital costs, and a 4.7-fold
increase in the odds of death.77 Published survival rates for
critically ill patients with cancer requiring renal replace-
ment therapy range from 20% to 50%.79,80 In particular,
patients with active hematological malignancies and renal
impairment have a poor prognosis, presumably because
renal impairment negatively affects optimal chemothera-
pic treatment.124 This was illustrated in a retrospective
study by Benoit et al, who found that, of 10 patients with
active disease who required dialysis, only one survived until
hospital discharge and died 80 days after ICU admission
because of refractory disease.79 Patients who are admitted
to the ICU because of neurologic complications have a
prognosis similar to that of critically ill patients who have
cancer without neurologic symptoms. A recent retrospec-
tive cohort study found an ICU mortality rate of 28% and a
hospital mortality rate of 37% in patients with a hemat-
ologic malignancy who were admitted to the ICU because of
a neurologic event.125 Furthermore, requirement of vasopres-
sors has also been found to confer a negative prognosis.117,126

The outcome of allogeneic stem cell transplant recipients
who require ICU treatment is still poor.110,127 In the 90s, the
mortality rate of patients after allogeneic stem cell transplan-
tation who were admitted to the ICU was typically above
90%.128,129 More recently, their survival has improved, but
mortality still remains high.130-133 The reported hospital mor-
tality of patients in studies that were published after 2010 is
in the range from 63% to 83%.127,131,134-137 Long-term sur-
vival is uniformly poor, with reported 1-year survival rates in
recent publications ranging from 15% to 19%.131,134,138 Of
note, a British retrospective, single-center study demonstrated
that, despite the poor outcome of critically ill allogeneic stem
cell transplantation recipients, those patients who did survive
the ICU stay achieved impressive 1-year and 5-year survival
rates of 61% and 51%, respectively, that were equivalent to
those of transplant recipients who did not require ICU admis-
sion.131 Admission during the conditioning phase and
reduced-intensity conditioning are associated with a lower
mortality.131,138 Especially those patients who suffer from
severe acute graft-versus-host disease and those who develop
respiratory failure with the need for mechanical ventilation
have a particularly high mortality rate.13,110,132,139-142 The
hematopoietic cell transplantation-specific comorbidity index
(HCT-CI) was identified as a good predictor of survival in
patients after allogeneic stem cell transplantation who were
admitted to the ICU.138 HCT-CI scores of 0 to 1, 2, 3, and
4, were associated with hospital survival rates of 54%, 33%,
37%, and 30%, respectively, and with corresponding 1-year overall survival rates of 22%, 17%, 18%, and 9%, respectively.

Because the majority of studies assessed short-term prognosis, relatively little is known about the long-term outcome of patients with cancer who need intensive care treatment. Recent studies suggest that the advances in long-term outcome are still lagging behind the success that has been achieved in short-term results, eg, survival to discharge from ICU (Fig. 1c).^87 Whereas short-term mortality is primarily determined by the severity of the acute illness, the long-term prognosis is decisively determined by characteristics of the underlying malignancy.88,143,144 Those studies that assessed long-term survival indicated that patients with cancer who were discharged alive from the ICU still had a high risk of mortality. A Spanish multicenter, prospective, observational study found that the mortality rate after discharge was 61%, with a median survival of 18 months.145 Patients who had a poor performance status (an Eastern Cooperative Oncology Group performance status >2) at the time of discharge from the ICU had a worse long-term survival.145 Staudinger et al reported that, despite an ICU survival rate of 53%, the 1-year survival rate of patients with cancer was only 23%,92 whereas the single-center study by Oyen et al demonstrated a better 1-year survival rate of 59%.87 The long-term survival of patients with metastatic solid tumors is particularly poor, with 1-year and 2-year survival rates of 12% and 2.4%, respectively.146 In those patients with cancer who survive their ICU stay, long-term quality of life is an important concern. Unfortunately, intensive care treatment is associated with reduced quality of life in survivors.87,147

Taken together, the data demonstrate that severity of disease is the major determinant of outcome in critically ill patients with cancer. Certain factors can identify patients with a worse prognosis but, by themselves, are insufficient to determine the prognosis of individual patients and the appropriateness of ICU admission for each patient.148,149 Therefore, prognostication of the chances of survival in critically ill patients with cancer is very challenging and entails a high degree of uncertainty.

**Admission Criteria and Admission Policy**

To find the right balance between providing critical care to patients with cancer who will benefit from intensive treatment while minimizing the inappropriate ICU admission of those who will have dismal outcomes, reliable tools of prognostication are needed. Most guidelines and recommendations of professional societies, such as the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, are outdated and contain little concrete advice for patients with cancer.18,150 Reliable, specific, evidence-based recommendations for the admission of patients with cancer are currently lacking. Many investigators have assessed the predictive value of different criteria for the selection of patients with cancer for ICU referral. General disease severity scores, such as APACHE II (Acute Physiology and Chronic Health Evaluation II), SAPS II (Simplified Acute Physiology Score II), or SOFA, perform poorly at informing the decision to admit individual patients with cancer to the ICU.99,102,151,152 Cancer-specific predictive models like the ICU cancer mortality model do not perform substantially better than the more general models.99,152,153 Currently, there is no single scoring system that has been sufficiently validated to be recommended for the triage of patients with cancer for ICU admission.

The inconsistent results regarding the prognostic value of many clinical parameters are likely a consequence of the considerable heterogeneity of the cancer patient population. Even if hematologic and solid tumors are considered separately, the remaining heterogeneity with regard to the type of cancer, available treatment options, concurrent comorbidities, and indications for ICU admission make comparisons between studies and the formulation of concrete conclusions and recommendations extremely difficult.154,155

The difficulty was illustrated by a French study in which physician’s judgment was identified as an unreliable predictor of outcome for critically ill patients with cancer.21 Of the patients who were considered too sick for ICU admission, according to the judgment of the intensivist, 26% and 16.7% were still alive after 30 and 180 days, respectively. Conversely, of the patients who were judged to be too well for ICU admission, 21.3% died within 30 days, most often after delayed ICU admission. These shortcomings of current predictors of patient trajectory speak for a broader ICU admission policy.

Although the mortality of critically ill patients with cancer is high, selected patient groups can profit from high-intensity treatment. On the basis of the literature, there are certain defined patient populations for which well-founded recommendations regarding admission to the ICU can be made (Table 2). Generally, critically ill patients with previously good performance status and curative treatment options should be admitted to the ICU. In contrast, in patients for whom no life-extending therapeutic options exist, ICU admission should be avoided unless intensive medical care is absolutely necessary to control symptoms. In practice, with the improved availability of palliative care services, this should rarely be necessary. For some patients who have incurable disease but an estimated survival of at least several months, limited intensive care treatment can be a valid option. These patients are offered certain aggressive treatment modalities, such as NIV or vasopressor support, while other interventions that are associated with a particularly poor prognosis, such invasive mechanical ventilation or cardiopulmonary resuscitation (CPR),
are excluded. Furthermore, ICU admission can be considered in patients for whom experimental treatments are available. This should be done only after careful assessment of the patient and cautious consideration of the likelihood that the patient will benefit from the experimental treatment. In many instances, the effectiveness of targeted therapies in critically ill patients is lower than that observed for patients in clinical trials. This was illustrated by a recent study in which patients with advanced cancer who received experimental treatments and were admitted to an ICU had a poor outcome.156 Notably, participation in clinical trials has been associated with more aggressive end-of-life care and worse quality of life near death.157

Some clinical factors define patient subgroups with a particularly dismal prognosis. For example, patients suffering from steroid-refractory, acute graft-versus-host disease have a low likelihood of a favorable outcome despite intensive care treatment.158 Likewise, elderly bedridden patients are poor candidates for ICU admission and are unlikely to benefit from aggressive life-sustaining treatment. Consequently, these patient groups should not be admitted to the ICU but instead should be offered palliative care.

With regard to the optimal time point, the current literature indicates that it would be desirable to admit critically ill patients with cancer as early as possible. Delayed or unplanned ICU admission results in increased mortality.16,31,159,160 Early ICU admission offers the opportunity to treat the patient before more serious damage has occurred. Aggressive treatment of early stage organ failure might prevent the development of multiorgan failure, which carries a very poor prognosis. Furthermore, late ICU admission has been associated with long-term functional impairment.161,162 Unfortunately, scoring systems, such as the modified early warning system (MEWS), have poor discriminatory power for identifying deteriorating patients.163 Patients with late ICU admission usually are more seriously ill and thus more often develop the need for vasopressor therapy or mechanical ventilation.164

In light of these findings, prophylactic ICU referral could represent a reasonable strategy for patients with a very high risk of clinical deterioration. Patients with newly diagnosed acute leukemia frequently develop life-threatening complications, such as leukostasis, coagulopathy, or tumor lysis syndrome, and reported ICU admission rates for these patients during induction chemotherapy are around 9% to 18%.144,165-167 Although some studies suggest that patients with acute myeloid leukemia may benefit from prophylactic ICU admission, currently, it would be premature to promote widespread adoption of this strategy outside of clinical trials.144,168

Given that there are no scores that can reliably predict the prognosis of individual critically ill patients with cancer, it seems reasonable to follow a permissive admission policy. The evolution of organ dysfunction in response to optimal critical care therapy may be a more reliable predictor of outcome than static parameters or scores that can be determined before admission.169 Rather than basing the decision to provide intensive care therapy on static parameters that can be assessed at the time of admission, the choice to continue full intensive medicine should be based on the trajectory of the patient’s condition. Lecuyer et al suggested an “ICU trial” strategy for patients with cancer who require

| Table 2. Admission Modalities for Critically Ill Patients With Cancer |
|---------------------------------------------------------------|
| **Full code (no restrictions in intensive care treatment)**    |
| • Newly diagnosed cancer and first-line therapy               |
| • Patients with cancer in complete remission                  |
| **ICU trial (initial full-code treatment with mandatory and repetitive reassessment starting 3–5 d after admission)** |
| • Potentially manageable cause of deterioration                |
| • Uncertainty about prognosis                                   |
| **Limited ICU therapy**                                        |
| • ICU therapy, eg, administration of vasopressors, with limitations such as no intubation and/or CPR |
| **Palliative (symptom management, no life-prolonging treatment)** |
| • Symptoms that cannot otherwise be controlled outside the ICU |
| **No admission (avoid ICU referral)**                          |
| • Patients who do not want aggressive treatment                |
| • Bedridden (ECOG >3, Karnofsky >30), elderly patients         |
| • Carcinomatous meningitis                                     |
| • Recurring/progressive disease without further treatment options |

CPR indicates cardiopulmonary resuscitation; ECOG, Eastern Cooperative Oncology Group; ICU, intensive care unit.
mechanical ventilation. This approach encompasses time-limited provision of full intensive care therapy with iterative reassessment of the patient’s condition at prespecified intervals. Although this approach seems promising, additional studies are warranted to confirm the value of the ICU trial strategy and to obtain further insight into how it should best be implemented. A recent simulation study aimed to identify the optimal duration of ICU trial with regard to short-term mortality in critically ill patients with cancer compared with the provision of time-unlimited intensive care. That study found that, for patients with cancer who had SOFA scores from 5 to 14, the optimal duration of ICU trial was 10 to 12 days. For sicker patients with SOFA scores >15, 8 days of ICU trial were sufficient. The study also found that 1 to 4 days may be sufficient for the subset of patients with solid tumors and a poor prognosis and that longer periods may be necessary for patients with hematologic malignancies.

What constitutes inappropriate ICU admission will likely remain a moving target. Because of the lack of validated criteria for ICU referral of patients with cancer, the decision of whether or not to admit has to be made on an individual basis. Patient-centered decision making with regard to ICU admission should take into account the wishes and values of the patient, the characteristics of the underlying malignancy, the available treatment options, the prognosis of the medical condition that requires ICU admission, and the expected long-term outcome and quality of life. If the circumstances permit, the decision to admit a critically ill patient with cancer ought to be made jointly by the referring oncologist and the intensivist. In making the decision to admit a patient with cancer to ICU, the interdisciplinary team should weigh the potential benefits of intensive care management against its potential to cause unnecessary suffering. In addition, they should define the goals of care and provide written documentation of the decision.

Management of Critically Ill Patients With Cancer in the ICU

Given the complexity of critical care for patients with cancer, it is not surprising that ICUs, which treat more critically ill patients with cancer, achieve better outcomes. To date, there are scarce data to make recommendations that are specific for the critical care management of patients with cancer. Many aspects of the management of critically ill patients with cancer have not been sufficiently addressed by clinical studies. For situations in which such patient-specific data are lacking, the management should follow the guidelines that exist for patients without neoplasms. Table 3 summarizes the most important principles in the intensive care management of critically ill patients with cancer.

In addition to intensive medical therapy, ICU admission should trigger an extensive diagnostic workup of the patient. Missed diagnoses with important therapeutic consequences are frequent in patients with cancer. In one-fourth to one-fifth of patients, there is a discrepancy between postmortem autopsy findings and premortem clinical diagnosis. Infections and cardiac disease are among the most common missed diagnoses.

Respiratory failure

Respiratory distress is the major reason for ICU referral of patients with cancer. Hypoxemia, extensive pulmonary infiltrates, and hemodynamic dysfunction are factors that identify patients with cancer who have a higher risk for intubation and mechanical ventilation. NIV is frequently recommended as the initial treatment of respiratory failure in patients with cancer. Older studies suggested that early introduction of NIV may prevent the development of acute respiratory failure and could improve survival. More recent studies did not confirm those earlier reports of a benefit from early NIV compared with oxygen therapy. NIV failure is more frequent in patients with cancer and is accompanied by a higher rate of intubation-associated complications and a worse prognosis, whereas early intubation is correlated with a better outcome.

Infection as the cause of acute respiratory failure, high respiratory rate under NIV, a longer delay between admission and initiation of NIV, a need for vasopressors or renal replacement therapy, and acute respiratory distress syndrome were identified as independent factors associated with NIV failure. In an analysis by Azoulay et al, patients who received NIV without subsequent invasive mechanical ventilation had a mortality rate of only 15%, whereas patients with late NIV failure had a mortality rate of 93% versus 78% in patients who received first-line invasive ventilation. Therefore, only patients who have isolated respiratory failure that is judged to be rapidly reversible should receive NIV. If NIV is indicated, it should be started early, and NIV success should be reassessed frequently. Exemplary indications for which a judicious trial of NIV could be considered include cardiogenic pulmonary edema or hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease. However, intubation should not be further delayed if NIV does not lead to prompt improvement of respiratory distress. NIV also remains a valid option for patients who have cancer with life-support technique limitations. Respiratory support with a humidified, high-flow nasal cannula represents a promising new tool for the management of patients with cancer who have respiratory distress. To determine the best strategy for the initial management of these patients, clinical trials comparing oxygen therapy, NIV, and mechanical ventilation are needed.
Infections and sepsis
Complications of cancer treatment are another important cause for consultation with intensive care specialists. Among the most frequent serious complications of current chemotherapeutic regimens are severe infections and sepsis caused by chemotherapy-induced neutropenia or direct immunosuppressive effects of treatment. Fortunately, the survival of patients with severe sepsis has improved substantially over the last decades.\textsuperscript{36,193} Early recognition and treatment of sepsis are keys to improving the outcome of septic patients with cancer. Many recent infectious disease guidelines acknowledge the special characteristics of patients with cancer and provide specific recommendations for the antimicrobial treatment of infections in patients with malignancies.\textsuperscript{194-201} Unlike the antimicrobial treatment of patients with severe infection, there are few specific recommendations with regard to the supportive care of these patients.\textsuperscript{202,203} Optimal management of patients with cancer with febrile neutropenia consists of prompt initiation of empiric antimicrobial treatment with broad-spectrum antibiotics. The choice of initial empiric antimicrobial agents should take into account the clinical presentation, the suspected source of infection, organ dysfunctions, and the local microbial spectrum and antibiotic resistance patterns.\textsuperscript{204} Approximately 15% of infections in patients with cancer are polymicrobial.\textsuperscript{205} Although prophylactic administration of G-CSF reduces the risk of febrile neutropenia in high-risk patients, G-CSF should not be routinely used in patients with established febrile neutropenia. Nonetheless, G-CSF can be considered in neutropenic patients who have infections and indicators of poor outcome.\textsuperscript{206}

Antineoplastic therapy in the ICU
Many patients with cancer who are admitted to the ICU need chemotherapy either for the initial treatment of their newly diagnosed cancer or as part of an ongoing treatment regimen. Recent reports show that approximately 5% of critically ill patients with cancer receive chemotherapy during their ICU stay.\textsuperscript{207} The ICU survival rate in those studies ranged between 60% and 67%. Studies furthermore demonstrated that chemotherapy could be given safely to selected critically ill patients with cancer.\textsuperscript{208,209} To date, many aspects of the administration of antineoplastic agents in the ICU setting, such as dose adjustment in the presence of organ failure, dosing during extracorporeal support like dialysis or extracorporeal membrane oxygenation, and

| TABLE 3. Summary of the Key Principles for the Management of Critically Ill Patients With Cancer From the Perspective of the Hematologist/Oncologist* |
|-----------------------------------------------|-----------------------------------------------|
| INTERVENTIONS | RECOMMENDATION |
| Before ICU admission | | |
| • Early integration of palliative care | D |
| • Administer anti-infective prophylaxis as recommended by guidelines | D |
| • Early identification of deteriorating patients and consultation of intensive care specialist/rapid response team | D |
| • Prophylactic ICU admission for initiation of induction chemotherapy in high-risk patients | C |
| • Postpone chemotherapy in the presence of life-threatening complications of cancer due to infection or organ dysfunction | N |
| • Strict ICU admission refusal of cancer patients with advanced disease | N |
| During ICU stay | | |
| • Close collaboration between hematologist/oncologist and intensivist | D |
| • Frequent reassessment of patient status, response to therapy, and prognosis | D |
| • ICU treatment according to guidelines for non-cancer ICU patients if no cancer-specific guidelines are available, eg, SSC guidelines | D |
| • Check for drug interactions with oncologic therapies | D |
| • Intensive communication with patient and relatives | D |
| • “ICU trial” when prognosis is uncertain | C |
| • Prolonged NIV in patients with respiratory failure who do not show signs of improvement | N |
| After ICU discharge | | |
| • Continue scheduled oncologic therapy as planned or with the least possible dose reduction | D |
| • Reassess treatment goals | D |
| • Screen for intensive care syndrome (PICS) | D |

ICU indicates intensive care unit; NIV, noninvasive support; PICS, postintensive care syndrome; SSC, Surviving Sepsis Campaign. *Recommendations are grouped chronologically in relation to the timing of ICU treatment. Letters indicate what to do (D), what to consider (C), and what not to do (N).
interactions with drugs commonly used in the ICU, have not been adequately studied.

Careful patient selection, appropriate choice of antineoplastic agents, tailored drug dosing, and close monitoring are key for the effective administration of antineoplastic therapy to critically ill patients. The benefits of administration of anticancer therapies to critically patients with malignancies have to be weighed against their potential to cause harm. Instead of prolonging survival, antineoplastic treatment may hasten death, especially if administered to unstable patients with organ dysfunction. The decision to administer antineoplastic treatment to critically ill patients has to be made on an individualized basis and should take into account the likelihood of response to therapy, long-term prognosis, as well as type and severity of organ dysfunction. A comprehensive overview of the current knowledge on dose adjustment in critically ill patients with cancer is provided in the review by Pitello et al.210

Several clinical factors have been identified that help in selecting critically ill patients who could benefit from the administration of chemotherapy in the ICU setting. Interestingly, active infection at the time of chemotherapy initiation is not an independent risk factor for ICU mortality.211 Furthermore, studies demonstrate that, after adjustment for differences in baseline characteristics, the outcome of severe sepsis or septic shock in patients with cancer is not negatively affected by chemotherapy.23,212 Thus, concurrent infection should not be viewed as a contraindication to the administration of chemotherapy to critically ill patients with malignancy. Not surprisingly, increasing severity of organ failure is associated with higher ICU mortality in patients who receive chemotherapy in the ICU.211,213 In particular, concurrent respiratory failure is accompanied by a poor outcome. However, the results of a prospective cohort study by Darmon et al in which the 30-day mortality rate was 32.5% for patients with acute leukemia who received full-dose chemotherapy irrespective of the presence of organ failure demonstrated that, in the ICU setting, the administration of high-dose chemotherapy is feasible despite organ dysfunction.213

In aggregate, the current body of evidence argues for early ICU admission of patients with cancer who show signs of organ failure or are at a high risk of clinical deterioration. The aim of early intensive care management should be to ensure that further deterioration and additional complications can be more rapidly recognized and managed. Furthermore, preventing the development of residual organ dysfunction through early aggressive therapy could improve the long-term outcome of chemotherapy, because patients who are unable to continue chemotherapy as scheduled after ICU discharge have a poor long-term prognosis.145,169

**Drug side effects**

Drug side effects and drug interactions are an important cause of morbidity and mortality in patients with cancer.214 In particular, severely sick patients with cancer who have organ dysfunction are at a high risk of developing adverse drug effects during the course of their ICU stay.214 Up to one-third of patients with cancer will experience serious side effects.214 Although they are mostly less toxic than current chemotherapeutic agents, most novel anticancer agents can also cause serious side effects that may require ICU admission (Table 4). Adverse effects can be because of on-target and off-target effects. For many of these adverse effects, there are no standard treatment algorithms. Therefore, management of the side effects of cancer therapy requires profound knowledge of the underlying mechanism of action. This will be even more important because the number of combination therapies will likely grow in the future. The example of chimeric antigen receptor T-cell–adoptive immunotherapy demonstrates that collaborative efforts of intensivists, oncologist, and translational researchers can facilitate the effective management of unexpected side effects of novel therapeutic agents.215

| DRUG | SIDE-EFFECT PROFILE |
|------|---------------------|
| Lenalidomide | Tumor flare reaction |
| Bevacizumab | Gastrointestinal perforation, hypertensive crisis |
| CAR T-cell immunotherapy | Cytokine storm, anaphylaxis |
| Venetoclax | Tumor lysis syndrome |
| ALK inhibitors | Pneumonitis |
| Ipilimumab | Autoimmune reactions (eg, colitis) |

Table 4. List of Serious Adverse Effects of Selected Novel Cancer Drugs

ALK indicates anaplastic lymphoma kinase; CAR, chimeric antigen receptor.
The pathophysiology of cytokine release syndrome is poorly understood. Occurrence of cytokine release syndrome is characterized by an increase of several proinflammatory cytokines, eg, interleukin-6 and interferon-γ. Other potentially life-threatening complications of immunotherapy are autoimmune reactions. It has been demonstrated that immune checkpoint inhibitors can precipitate severe and, if inadequately treated, fatal autoimmune reactions, such as colitis and adrenal insufficiency.

It has also been demonstrated that immunosuppressive treatment with corticosteroids or the administration of anticytokine therapies can dampen the inflammatory reaction that is part of the cytokine release syndrome or immunotherapy-induced autoimmunity. However, anti-inflammatory treatment can have the unwanted consequence of inhibiting antitumor effector mechanisms, thereby limiting the efficacy of immunotherapeutic agents. Therefore, the treatment of immunotherapy-associated immune reactions ideally has to be finely tuned to minimize detrimental side effects for the patient while maximizing immunotherapeutic activity. Fortunately, attempts to develop standardized protocols for the treatment of these immunologic side effects are starting to emerge.216

CPR

Patients with malignant disease are considered poor candidates for CPR.217-219 The outcome of CPR in patients with cancer is worse than in patients without cancer, and those with incurable cancer rarely survive after in-hospital CPR.220,221 A meta-analysis demonstrated that the rate of survival to hospital discharge for patients with localized or metastatic disease reaches 9.5% and 6.2%, respectively.222 These survival rates are even more discouraging if one considers that patients who received CPR already constitute a selected subgroup from which patients with the worst prognosis were already excluded because they had a do not resuscitate (DNR) order in place. More recent reports suggest that the outcome of patients with cancer after CPR may have improved slightly.223,224

The chances of survival are affected by several clinical factors. Acute renal failure, being on mechanical ventilation, refractory shock, performance status, and CPR duration are predictive of resuscitation failure.225,226 Patients with cancer who had sudden, unexpected cardiac arrest had a substantially higher chance of survival until discharge than patients in whom cardiac arrest was anticipated.227 The poor prognosis of patients with cancer after CPR highlights the importance of end-of-life discussions for the subsequent provision of intensive care. These discussions ideally should be initiated early in the disease process to prevent futile resuscitative efforts. Studies confirm that interventions that aim to enhance the patient’s understanding of CPR by provision of information through personal discussion and information leaflets increase the percentage of patients who forgo resuscitation and result in more frequent and earlier placement of DNR orders.228,229

Transitioning to End-of-Life Care

High-quality end-of-life care is a crucial part of exceptional cancer critical care.230 When asked about their preferences, the large majority of patients would like to die at home and not in hospital.231 Unfortunately, oftentimes there is a disconnect between the patient’s preferences and the actual care they receive. As a consequence, the majority of patients with cancer die in hospital; and, of those deaths, many occur in the ICU.232,233 Bekelman et al recently reported that, in developed countries, between 3.5% and 27.2% of all elderly patients with cancer had at least one ICU admission during their last 30 days of life.234 According to the Dartmouth Atlas Project, approximately one-fourth of patients with cancer in the United States are admitted to intensive care at least once during their last month of life.235 The transition from full intensive care treatment to end-of-life care is a complex process. Reframing the focus of care from cure to comfort can be problematic for the patients, their families, and health care providers.

There is considerable variation with regard to the limitation of life-sustaining therapies in the ICU. Several studies have demonstrated a surprising degree of geographic variation in the frequency of withholding or withdrawal of life-prolonging treatment.236 Moreover, apart from local policies, physician beliefs and attitudes are likely major determinants of variability in the prevalence of decisions to forgo intensive care treatment in end-of-life situations.237,238

Early discussions about goals of care and end-of-life topics frequently can ease the transition to end-of-life care and reduce psychosocial distress among patients and family members. In addition, discussions about treatment goals and end-of-life preferences can give patients the opportunity to affect the care they desire near the end of life. It has been shown that end-of-life discussions and advance care planning can reduce the use of aggressive care in the last weeks of life.239,240 Remarkably, patients with cancer who opted for life-extending treatment and received care in the last weeks of their life that was consistent with their preferences had a lower quality of life and higher physical and psychosocial distress than patients who requested life-extending care but ultimately did not receive it.241,242 Less intense care at the end of life was associated with better quality of life of the patient and also led to better quality of life for family caregivers.239,243

The patient’s primary oncologic care team can have a decisive influence on the transition to end-of-life care. Clinicians should try to discuss end-of-life issues and palliative care with patients who have cancer early after
diagnosis to avoid futile care. Nonetheless, in practice, there are several barriers that prevent adequate discussion of prognosis and advance care planning. Discussions about advance care planning often are difficult, time-consuming, and may not be adequately compensated. Therefore, it is not surprising that the majority of oncologists postpone discussions until all chemotherapeutic options are exhausted. Therefore, studies demonstrate that, even after ICU admission, in about one-third of cases, the patient’s preferences regarding goals of care and withdrawal of therapy are not discussed.245,246

There are several factors that can impair the critically ill patient’s capacity to make an informed decision. The ability of the patient to participate in shared decision making can be compromised by difficulties in understanding the nature of the malignant disease and the implications of therapy. Many patients with advanced cancer have difficulties comprehending the noncurative intent of palliative therapy.247 They often opt for chemotherapy and are willing to accept considerable toxicity for small benefits.248 To make things even more complex, the patient’s attitude to goals of treatment may change over time. Therefore, end-of-life discussion and advanced care planning should be viewed as a continuous process.249 Oftentimes the patients are to sick and cannot formulate their wishes and participate in discussions about treatment choice. As a consequence, family members often play a critical role in the decision-making process.250 Thus communication with families is an important aspect of critical care for patients with cancer.

The patient’s oncologist should be involved whenever the need to discuss the limitations of life support arises, and the decision to forgo or withdraw life-sustaining therapy should be made after discussion of the case by an interdisciplinary team involving a critical care specialist and an oncologist. Whenever possible, unanimity both among the care team and with the patient or their surrogate should be sought before the withdrawal of life-sustaining treatment. In cases where there is disagreement between the ICU team and the patient or their surrogate about withholding or withdrawing of life-sustaining therapy, consultation of a clinical ethics committee can be helpful and has been shown to be able to resolve conflicts in the majority of cases.251

Impact on Patients, Relatives, and Caregivers

Intensive care treatment of critically ill patients with cancer can have a negative impact on the patient, their family, and the members of the ICU team. Aside from the potential quantity of life that could be gained, these negative effects should also be taken into consideration in the decision to admit a critically ill cancer patient to the ICU.252 As a consequence of prognostic uncertainty, the treatment of patients with cancer in the ICU setting is particularly prone to conflicts. Each of the different stakeholders has their own perspective and needs, and a better understanding of their distinct perspectives could help to improve the satisfaction of patients with cancer and their relatives and caregivers.

The experience of ICU treatment is an incisive event for the patient and family members. Spending the last weeks of life in the ICU is associated with worse quality of life and more physical and emotional distress for both patients and caregivers.253 Study results show that patients who were admitted to the ICU had a lower quality of life and were more burdened by their symptoms in the weeks before their death. However, patients often underestimate the burden of aggressive treatment at the end of life, and many patients are willing to accept considerable toxicity for small increases in life expectancy.

Treating physicians have to be aware that critical care treatment can have long-term adverse effects that affect the patient’s quality of life long after discharge from the ICU. Many ICU survivors suffer from postintensive care syndrome, which consists of a range of physical, mental, and emotional health problems that persist beyond hospitalization. Persistent functional disabilities include ICU-acquired weakness, cognitive dysfunction, and symptoms of posttraumatic stress disorder.162,254,255 ICU-acquired weakness makes it difficult for patients to perform activities of daily living and prevents them from participating in social life. In addition, a large fraction of ICU survivors who are discharged from hospital—in some studies, up to 43%—are not discharged home but instead are transferred to a nursing home.256

As the longer term psychological and physical impact of intensive care on those surviving acute critical illness is increasingly documented, the patients and their relatives need to be prepared for challenges that can occur after discharge from the ICU. However, a growing body of evidence indicates that long-term reductions in quality of life are not necessary and that some patients can benefit from intensive care treatment without the fear of long-term sequelae.257

The experience of a relative’s ICU stay can have long-lasting adverse health effects for family members of a patient with cancer.258 The burden of the cancer diagnosis and the participatory role in decision making can cause anxiety, depression, and symptoms of posttraumatic stress disorder in the relatives of patients with cancer.259,260 Depressive symptoms among family members have a prevalence of approximately 75% during critical care and 25% after 1 year.261

Caring for critically ill patients with cancer can also represent a considerable psychological burden for the health care providers of the patient, eg, physicians and nurses. Psychosocial distress is a frequent problem among health care
professionals in ICUs.\textsuperscript{262} Discrepancies in perspective and medical knowledge are important underlying causes for disagreement, frustration, and conflict within the ICU team.\textsuperscript{263,264} Perceived inappropriate care and a lack of inclusion in the decision-making process are frequent sources of disagreement and conflict.\textsuperscript{265}

Taken together, current research results emphasize the importance of communication for the quality of care and satisfaction of the affected patients, families, and health care professionals with the care provided to critically ill patients with cancer.\textsuperscript{266} Effective communication plays a central role in intensive care management of these critically ill patients and is a key factor that shapes the organizational climate. A culture of mutual respect and open discourse in which areas of disagreement and moral distress can be openly discussed serves to mitigate frustration and improve satisfaction. Improving discussions with patients and families as well as within the ICU team is pivotal to improving moral distress and the quality of patient care. Regular meetings and discussions have been shown to reduce psychosocial distress and burnout among relatives and health care workers on ICUs.\textsuperscript{267}

Economic Aspects

The costs of cancer care are projected to increase in coming decades.\textsuperscript{268} Progress in the treatment of cancer has been accompanied by an increase in health care expenditures for oncologic drugs.\textsuperscript{269} These cost increases will place an enormous financial strain on health care systems and call into question the sustainability of high-quality cancer care. In the United States, it is expected that, by 2020, the total cost of cancer care will reach \$173 billion or approximately 20\% of the gross domestic product.\textsuperscript{270} The rising costs are a consequence of the demographic changes and the development of novel diagnostic tools and therapeutic modalities. Modern oncologic therapies come at a high cost, which is further potentiated by the expenditures for intensive care treatment. In the United States, critical care medicine was responsible for 13.3\% of total hospital costs and 4.2\% of total health care expenditures in the year 2000.\textsuperscript{271} The impending threat of escalating costs for modern cancer treatment raises issues about the optimal allocation of limited financial health care resources. Furthermore, in many health care systems, the costs of cancer therapy represent a considerable financial toxicity to the patients and their families.\textsuperscript{272,273} In the future, high costs will force the treating oncologists and intensive care specialists to integrate cost considerations into the decision-making process.

Intensive care treatment for patients with cancer is associated with higher resource use and cost.\textsuperscript{35,274-276} There are scant data to inform health care policy with regard to the provision of cost-effective, high-quality intensive care to critically ill patients with cancer. Higher spending for end-of-life care does not necessarily mean better care. In fact, higher costs of treatment in the last weeks of life can be related to a worse quality of death, whereas conversation about the goals of treatment and end-of-life issues are associated with reductions in the cost of care.\textsuperscript{277}

The widespread implementation of cancer critical care will require changes in health care policy and reimbursement systems to enable the provision of high-class care for the sickest patients with cancer while minimizing the financial burden on patients and society. The cost effectiveness of critical care medicine for patients with cancer depends on the ability to reliably predict who will benefit from aggressive treatment. Improved ICU admission systems will have cost-saving effects and will lead to the better utilization of scarce ICU resources by avoiding medically inappropriate and costly treatments.\textsuperscript{276} To achieve this goal, financial compensation for many nontechnical aspects of critical care that currently are not adequately reimbursed has to be improved. In the end, these changes will likely pay off both with regard to the quality improvements they enable and also in terms of cost savings through a reduction in unwarranted ICU admissions.\textsuperscript{240,278} The money saved by avoiding costly but futile therapy could at least partly offset the increased cost of providing potentially lifesaving intensive care to selected critically ill patients with cancer.

Future Outlook

Faced with the rapid development of both intensive care and oncology, cancer critical care will continue to undergo dynamic development. Technological innovations in critical care will make it possible to provide less invasive life support and will likely translate into further improvement in survival for critically ill patients with cancer.\textsuperscript{30} This progress will bring about a sizable growth in the number of critically ill patients with cancer who qualify for intensive care treatment. Developing countries will face especially challenging problems.\textsuperscript{279} Care for critically ill patients with cancer places a relatively higher burden on developing countries than on developed countries. Therefore, how those countries will be able to provide high-value care to patients with cancer will remain a challenging problem.

The field of cancer critical care is still in its infancy, and there remain many areas of uncertainty. Therefore, research that focuses on a better understanding of the specifics of critical care for patients with cancer is urgently needed. This type of research will require a novel form of collaborative infrastructure that brings together oncologists, intensivists, and palliative care specialists. Priorities should be to find the best ways to select patients who benefit from ICU admission and to fill the evidence gaps regarding the optimal clinical management of critically ill patients.
with cancer. Therefore, prospective studies addressing questions that are unique to the care of these critically ill patients are urgently required. Instead of short-term outcome, future studies should focus on long-term survival and more direct outcome measures, including family satisfaction or quality of life after ICU or hospital discharge. Another area of need is the discovery of strategies to improve the ICU experience for patients with cancer. Because it will not be possible to completely prevent death in the ICU, it will be necessary to explore novel approaches to eliminate suffering and improve the quality of dying in the ICU.

The constantly changing landscape of cancer therapy will make it necessary to regularly reevaluate existing evidence for the selection and treatment of critically ill patients with cancer in light of novel therapeutic options in oncology and critical care. Therefore, future research should explore novel concepts for the integration of critical care into cancer therapy in the era of precision medicine. We need a better understanding of how the availability of more targeted and more effective cancer therapies affect ICU admission criteria and intensive care management of critically ill patients with cancer. The challenges posed by the rising costs of providing intensive therapy to these patients necessitate further research. Insights from this research will help to deliver evidence-based, high-quality, and equitable patient-centered care, thereby helping to ensure better quality of life and limiting costs.

Future progress in the field of critical care for patients with cancer will require the establishment of a specialized infrastructure that fosters the conduction of clinical trials as well as provision of formal training opportunities and implementation of research findings into clinical practice. Large comprehensive cancer centers will likely be the driving force behind these developments. These specialized centers with expertise in cancer critical care will take a central role in the dissemination of evidence-based management strategies for critically ill patients with cancer.

Conclusion

Comprehensive care for critically ill patients with cancer is a collaborative effort, and close cooperation between oncology as well as palliative and critical care is essential. Collaborative decision making is a cornerstone of high-quality critical care for patients with cancer. Like palliative medicine, critical care should be integrated early and seamlessly into the management of these patients. This will facilitate the early identification of patients who will most likely profit from aggressive management and the provision of optimal palliative care to those who are unlikely to benefit from intensive care. The ultimate goal should be to provide every critically ill patient who has cancer with high-quality critical care that is as tailored to his or her needs and personal preferences as the drugs that are used to treat their tumor.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.
3. Tanveyanal E, Leighton JC. Life-sustaining treatments in patients who died of chronic congestive heart failure compared with metastatic cancer. Crit Care Med. 2003;31:60-64.
4. Fan E, Gattianni L, Combes A, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory failure: a clinical review from an international group of experts. Intensive Care Med. 2014;40:172-724.
5. Masters GA, Krilov L, Bailey HH, et al. Clinical cancer advances 2015: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol. 2015;33:786-809.
6. Hawgood S, Hook-Barnard IG, O’Brien TC, Yamamoto KR. Precision medicine: beyond the inflection point [serial online]. Sci Transl Med. 2015;7:300ps17.
7. Schwaerdele M, Zhao M, Lee JJ, et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. J Clin Oncol. 2015;33:3817-3825.
8. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell. 2015;161:205-214.
9. Azoulay E, Thiery G, Chevret S, et al. The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore). 2004;83:360-370.
10. Puxty K, McLoone P, Quasim T, Sloan B, Kinsella J, Morrison DS. Risk of critical illness among patients with solid cancers: a population-based observational study. JAMA Oncol. 2015;1:1078-1085.
11. Gordon AC, Oakervee HE, Kaya B, et al. Incidence and outcome of critical illness amongst hospitalised patients with haematological malignancy: a prospective observational study of ward and intensive care unit based care. Anaesthesia. 2005;60:340-347.
12. Bos MM, Verburg I, Dumaai L, et al. Intensive care admission of cancer patients: a comparative analysis. Cancer Med. 2015;4:966-976.
13. Benz R, Schanz U, Maggiorini M, Seebach JD, Stussi G. Risk factors for ICU admission and ICU survival after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2014;49:62-65.
14. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and outcomes of cancer patients in European ICUs [serial online]. Crit Care. 2009;13:R15.
15. Soares M, Caruso P, Silva E, et al. Characteristics and outcomes of patients with cancer requiring admission into intensive care units: a prospective multicenter study. Crit Care Med. 2010;38:9-15.
16. Bos MM, de Keizer NF, Meynaar IA, Bakhshi-Raiez F, de Jonge E. Outcomes of cancer patients after unplanned admission to general intensive care units. Acta Oncol. 2012;51:897-905.
17. Carlson GC. Admitting cancer patients to the intensive care unit. Crit Care Clin. 1998;4:183-191.
18. Guidelines for intensive care unit admission, discharge, and triage. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Crit Care Med. 1999;27:633-638.
19. Guidelines for developing admission and discharge policies for the pediatric intensive care unit. Pediatric Section Task Force on Admission and Discharge Criteria, Society of Critical Care Medicine in conjunction with the American College of Critical Care Medicine and the Committee on Hospital Care of the American Acad-
eny of Pediatrics. Crit Care Med. 1999;27:843-845.

20. Garrouste-Orgeas M, Montuclard L, Timsit JF, et al. Predictors of intensive care unit refusal in French intensive care units: a multiple-center study. Crit Care Med. 2003;31:750-755.

21. Thiery G, Azoulay E, Darmon M, et al. Outcomes of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol. 2005;23:4406-4413.

22. Benoit DD, Depuydt PO. Outcome in critically ill cancer patients: past and present. Rev Bras Ter Intens. 2008;20:847-87.

23. Cherif H, Martling C-R, Hansen J, Kalin M, Bjorkholm M. Predictors of short and long-term outcome in patients with hematological disorders admitted to the intensive care unit for a life-threatening complication. Support Care Cancer. 2007;15:1393-1398.

24. Agarwal S, ODonoghue S, Gowdard J, Kennedy G, Bandeshe H, Boots R. Intensive care unit experience of haemopoietic stem cell transplant patients. Intern Med. 2012;42:748-754.

25. Boehm A, Rabbitsch W, Locker GJ, et al. Successful allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia during respiratory failure and invasive mechanical ventilation. Wien Klin Wochenschr. 2011;123(11-12):354-358.

26. Gorjup V, Fister M, Noc M, Rajic V, Ribaric SF. Treatment of sepsis and ARDS with extracorporeal membrane oxygenation and interventional lung assist membrane ventilator in a patient with acute lymphoblastic leukemia. Respir Care. 2012;57:1178-1181.

27. Ahn HK, Jeon K, Yoo H, et al. Successful treatment with crizotinib in mechanically ventilated patients with ALK-positive non-small-cell lung cancer. J Thorac Oncol. 2013;8:250-253.

28. Ordemann R, Stohlmaczer J, Beuthien-Baumann B, et al. Use of targeted therapy for refractory ALK-positive anaplastic large cell lymphoma as a bridging strategy prior to allogeneic transplantation. Ann Hematol. 2013;92:125-127.

29. Adam V, Doms C, Vansteenkiste J. Lung cancer at the intensive care unit: the era of targeted therapy. Lung Cancer. 2015;89:218-221.

30. Wohlfarth P, Ulrich R, Staudinger T, et al. Extracorporeal membrane oxygenation in adult patients with hematologic malignancies and severe acute respiratory failure [serial online]. Crit Care. 2014;18:R20.

31. Peigne V, Rusinova K, Karlin L, et al. Continued survival gains in recent years among critically ill myeloma patients. Intensive Care Med. 2009;35:512-518.

32. Algrin C, Faguer S, Lemiaile V, et al. Outcomes after intensive care unit admission of patients with newly diagnosed lymphoma. Leuk Lymphoma. 2015;56:1240-1245.

33. Lloyd-Thomason AR, Wright I, Lister TA, Hinds CJ. Prognosis of patients receiving intensive care for life-threatening medical complications of haematological malignancy. BMJ (Clin Res Ed). 1988;296:1025-1029.

34. 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.

35. Schapira DV, Studnicki J, Bradham DD, Wolff P, Jarasho I. Intensive care, survival, and expense of treating critically ill cancer patients. JAMA. 1993;269:783-786.

36. Pene F, Percheron S, Lemiale V, et al. Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med. 2008;36:690-696.

37. Zuber B, Tran TC, Aegerter P, et al. Impact of case volume on survival of septic shock in patients with malignancies. Crit Care Med. 2012;40:55-62.

38. Benoit DD, Soares M, Azoulay E. Has survival increased in cancer patients admitted to the ICU? We are not sure. Intensive Care Med. 2014;40:1576-1579.

39. Mokart D, Pastores SM, Darmon M. Survival increased in cancer patients admitted to the ICU. Yes. Intensive Care Med. 2011;40:1570-1572.

40. Pene F, Sallab JF, Staudinger T. Has survival increased in cancer patients admitted to the ICU? No. Intensive Care Med. 2014;40:1573-1575.

41. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. Curr Opin Crit Care. 2012;18:700-706.

42. Kim MM, Barnato AE, Angus DC, Fleisher LF, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. Arch Intern Med. 2010;170:369-376.

43. Jones DA, DeVita MA, Bellomo R. Rapid-response teams and improving standards. Crit Care Med. 2012;40:1573-1575.

44. Song JU, Suh GH, Park HY, et al. Early intervention on the outcomes in critically ill cancer patients admitted to intensive care unit. Intensive Care Med. 2012;38:1505-1513.

45. Parmar A, Richardson H, McKinlay D, Gibney RT, Bagshaw SM. Medical emergency team involvement in patients hospitalized with acute myeloid leukemia. Leuk Lymphoma. 2013;54:2236-2242.

46. Tam B, Salib M, Fox-Robichaud A. The effect of rapid response teams on end-of-life care: a retrospective chart review. Can Respir J. 2014;21:302-306.

47. Nelson JE, Mathews KS, Weissman DE, et al. Integration of palliative care in the context of rapid response: a report from the Improving Palliative Care in the ICU advisory board. Chest. 2015;147:560-569.

48. Clare P, Virki K, Jones M, et al. A systematic review of physicians’ survival predictions in terminal ill cancer patients. BMJ. 2005;327:195-198.

49. Clement-Duchene C, Carmin C, Guillemin F, Martinot V. How accurate are physicians in the prediction of patient survival in advanced lung cancer? Oncologist. 2010;15:782-789.

50. Kao SC, Butow P, Bray V, Clarke SJ, Vardy J. Patient and oncologist estimates of survival in advanced cancer patients. Psychooncology. 2011;20:213-218.

51. Gwilliam B, Keeley V, Todd C, et al. Prognosticating in patients with advanced cancer—observational study comparing the accuracy of clinicians’ and patients’ estimates of survival. Ann Oncol. 2013;24:482-488.

52. Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. Ann Intern Med. 2001;134:1096-1105.

53. Hsia TC, Tu CY, Chen HJ. The impact of rescue or maintenance therapy with EGFR TKIs for stage IIIb-IV non-squamous non-small cell lung cancer patients requiring mechanical ventilation [serial online]. BMC Anesthesiol. 2014;14:55.

54. O’Brien JM, Aberreg SK, Ali NA, Diette GB, Lemeshow S. Results from the National Sepsis Practice Survey: predictions about mortality and morbidity and recommendations for limitation of care orders [serial online]. Crit Care. 2009;13:R96.

55. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. J Clin Oncol. 2012;30:880-887.

56. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363:733-742.

57. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol. 2015;33:1438-1445.

58. Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. Cancer. 2014;120:1743-1749.

59. Dionne-Odom JN, Azenzo A, Lyons KD, et al. Benefits of early versus delayed palliative care to informal family caregivers of patients with advanced cancer: outcomes from the ENABLE III randomized controlled trial. J Clin Oncol. 2015;33:1446-1452.

60. Greer JA, Jackson VA, Meier DE, Temel JS. Early integration of palliative care services with standard cancer care for patients with advanced cancer. CA Cancer J Clin. 2013;63:349-363.

61. Jang RW, Krzyzanowska MK, Zimmermann C, Taback N, Alibhai SM. Palliative care and the aggressiveness of end-of-life care in patients with advanced pancreatic cancer [serial online]. J Natl Cancer Inst. 2015;107. pii: dju424.

62. Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: pathophysiolog- y, presentation, diagnosis, and treatment. CA Cancer J Clin. 2011;61:287-314.

63. Darmon M, Vincent F, Camous L, et al. Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multic- ician study from the Groupe de Recher- che en Reanimation Respiratoire et Onco- Hematologique. Br J Haematol. 2013;162:489-497.

64. Lyman GH, Bohle K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology
clinical practice guideline update 2014. J Clin Oncol. 2015;33:654-656.

65. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit Care. 2004;8:R291-R298.

66. Pastores SM, Voigt LP. Acute respiratory failure in the patient with cancer: diagnostic and management strategies. Crit Care Clin. 2010;26:21-40.

67. Soares M, Depuydt PO, Salluh JJ. Mechanical ventilation in cancer patients: clinical characteristics and outcomes. Crit Care Clin. 2010;26:41-58.

68. Chi AK, Soubani AO, White AC, Miller KB. Predictors and outcome of acute kidney injury in patients with hematopoietic stem cell transplantation. Chest. 2013;144:1913-1922.

69. Azoulay E, Lemaile V, Mokart D, et al. Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med. 2014;40:1106-1114.

70. Todeschini G, Murari C, Boneci R, et al. Invasive aspergillosis in neutropenic patients: rapid neutrophil recovery is a risk factor for severe pulmonary complications. Eur J Clin Invest. 1999;29:453-457.

71. Rhee CK, Kang JY, Kim YH, et al. Risk factors for acute respiratory distress syndrome during neutropenia recovery in patients with hematologic malignancies [serial online]. Crit Care. 2009;13:R173.

72. Azoulay E, Darmon M, Delclaux C, et al. Deterioration of previous acute lung injury during neutropenia recovery. Crit Care Med. 2002;30:781-786.

73. Karlin L, Darmon M, Thiery G, et al. Worsening of respiratory status during neutropenia recovery in patients with hematologic malignancies [serial online]. Crit Care. 2009;13:R173.

74. Balsot M, Xhaard A, Lengline E, et al. Osteomyelitis in patients with hematologic malignancies: results of a prospective multicenter study. Respiration. 2015;90:229-234.

75. Moreau AS, Lengline E, Seguin A, et al. Respiratory status deteriorating during neutropenia recovery in patients with hematologic malignancies. Chest. 2013;145:110-117.

76. Lahoti A, Kantarjian H, Salahudeen AK, et al. Acute kidney injury in patients with acute myelogenous leukemia. Leuk Lymphoma. 2014;55:2556-2563.

77. Lahoti A, Kantarjian H, Salahudeen AK, et al. Prognosticators of acute kidney injury in lymphoma: a single centre experience. Int J Hematol 2014;99:27961, 2014.

78. 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 hematological malignancies. Nephrol Dial Transplant. 2005;20:552-558.

79. Heeg M, Mertens A, Ellenberger D, Muller GA, Patschan D. Prognosis of AKI in malignant diseases with and without sepsis [serial online]. BMC Anesthesiol. 2013;13:36.

80. Lameire NH, Flombaum CD, Moreau D, Ronco C. The renal function in cancer patients. Ann Med. 2005;37:13-25.

81. Soares M, Salluh JI, Carvalho MS, Darmon M, Rocco J, Salluh JI. Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol. 2006;24:4003-4011.

82. Lam AQ, Humphreys BD. Onco-nephrology: AKI in the cancer patient. Clin J Am Soc Nephrol. 2012;7:1692-1700.

83. Zeng X, McMahon GM, Brunelli SM, Oliver BG, Chalmers JD, Bates DW, Waikar SS. Incidence, outcomes, and associations of AKI in patients admitted to a comprehensive cancer care center. J Am Soc Nephrol. 2014;25:153-160.

84. Williams MD, Braun LA, Cooper LM, et al. Acute kidney injury in lymphoma: a single centre experience. Int J Hematol 2014;99:27961, 2014.

85. Bissell L, Khan OA, Mercer SJ, Somers SS, Toh SK. Long-term outcomes following emergency intensive care admission after elective oesophagectomy. Acta Chin Belg. 2013;113:14-18.

86. Song SW, Lee HS, Kim JH, Kim MS, Lee SM. Long-term outcomes of intensive care unit after initial recovery from major thoracic surgery. Korean J Thorac Surg. 2007;84:1838-1846; discussion 1838–1846.

87. Soares M, Fontes F, Dantas J, et al. Perioperative performance of six severity-of-illness scores in cancer patients requiring admission to the intensive care unit: a prospective observational study. Crit Care. 2004;8: R194-R203.

88. 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.

89. Souza-Dantas VC, Salluh JIF, Soares M. Impact of neutropenia on the outcomes of critically ill patients with cancer: a matched case-control study. Ann Oncol. 2011;22:2094–2100.

90. Bird GT, Farquhar-Smith P, Wigmore T, Potter M, Gruber PC. Outcomes and prognostic factors in patients with haematological malignancy admitted to a specialist cancer intensive care unit: a 5 yr study. Br J Anaesth. 2012;108:452-459.

91. Mokart D, Darmon M, Resche-Rigon M, et al. Prognosis of neutropenic patients admitted to the intensive care unit. Intensive Care Med. 2015;41:296-303.

92. Depuydt PO, Benoit DD, Vandewoude KH, Decruyenaere JM, Colardyn FA. Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. Chest. 2004;126:1299-1306.

93. Benoit DD, Depuydt PO, Peelman RA, et al. Documented and clinically suspected bacterial infection precipitating intensive care unit admission in patients with haematological malignancies: impact on outcome. Intensive Care Med. 2005;31:934-942.

94. Vandijck DM, Depuydt PO, Offer NJ, et al. Impact of organ dysfunction on mortality in ICU patients with hematologic malignancies. Intensive Care Med. 2010;36:1744-1750.

95. Ewig S, Torres A, Riquelme R, et al. Pulmonary complications in patients with haematological malignancies treated at a respiratory ICU. Eur Respir J. 1998;12:116-122.

96. Huynh TN, Weigt SS, Belperio JA, Territo CA. Pathogenesis and associated costs of care. Curr Oncol. 2015;32:496-517.
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111. Kerhuel L, Amorim S, Azoulay E, Thieblemont C, Canet E. Clinical features of life-threatening complications following autologous stem cell transplantation in patients with lymphoma. Leuk Lymphoma. 2015;56:1590-3095.

112. Soares M, Carvalho MS, Salluh JI, et al. Effect of age on survival of critically ill patients with cancer. Crit Care Med. 2006;34:715-721.

113. Mokart D, Granata A, Roberto C, et al. Allogeneic hematopoietic stem cell transplantation after reduced intensity conditioning regimen for outcomes of patients admitted to intensive care unit. J Crit Care. 2015;30:1107-1113.

114. Cornet AD, Issa AI, van de Loosdrecht AA, Mokart D, Granata A, Roberto C, et al. Malignancy patients with invasive pulmonary aspergillosis. Intensive Care Med. 2004;30:1718-1823.

115. Blot F, Guiguet M, Nitenberg G, Leclercq G, Groeger JS, Lemeshow S, Price K, et al. Hemodialysis for acute renal failure in patients with hematologic malignancy needing intensive care. Eur J Haematol. 1997;33:1031-1037.

116. 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.

117. Groeger JS, Lemeshow S, Price K, et al. Multicenter case-control study of outcome in critically ill patients admitted to the intensive care unit: a probability of mortality model. J Clin Oncol. 1998;16:761-770.

118. Burghi G, Lemiale V, Seguin A, et al. Outcomes of mechanically ventilated hematological patients with invasive pulmonary aspergillosis. Intensive Care Med. 2011;37:1605-1612.

119. Shih CY, Hung MC, Lu HM, Chen L, Huang SJ, Wang JD. Incidence, life expectancy and prognostic factors in cancer patients under prolonged mechanical ventilation: a nationwide analysis of 5,138 cases during 1998–2007 [serial online]. Crit Care. 2013;17:R144.

120. Canet E, Zafrañi L, Lambert J, et al. Acute kidney injury in patients with newly diagnosed high-grade hematological malignancies: impact on remission and survival [serial online]. PLoS One. 2013;8:e55870.

121. Maccariello E, Valente C, Nogueira L, et al. Outcomes of cancer and non-cancer patients with acute kidney injury and need of renal replacement therapy admitted to general intensive care units. Nephrol Dial Transplant. 2011;26:537-543.

122. Samuels J, Ng CS, Nates J, et al. Small amount of serum creatinine are associated with prolonged ICU stay and increased hospital mortality in critically ill patients with cancer. Support Care Cancer. 2011;19:1527-1532.

123. Darmon M, Cirolitti M, Thierry G, Schlembner B, Azoulay E. Clinical review: specific aspects of acute renal failure in cancer patients [serial online]. Crit Care. 2006;10:211.
153. 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.

154. Berghmans T, Sculier JP. Is there any usefulness for a specific scoring system in assessing the prognosis of cancer patients admitted to the intensive care unit [letter]? *Intensive Care Med.* 2004;30:1849; author reply 1850.

155. Puxty K, McLoone P, Quasim T, KinSELLA J, Morrison D. Survival in solid cancer patients following intensive care unit admission. *Intensive Care Med.* 2014;40:1409-1428.

156. Fu S, Hong DS, Naing A, et al. Outcome analyses after the first admission to an intensive care unit in patients with advanced cancer referred to a phase I clinical trials program. *J Clin Oncol.* 2011;29:3547-3552.

157. Enzinger AC, Zhang B, Weeks JC, PriGerson HG. Clinical trial participation as part of end-of-life cancer care: associations with medical care and quality of life near death. *J Pain Symptom Manage.* 2014;47:1078-1090.

158. Cooksley T, Kitlowski E, Haji-Michael P, De Jonghe B, Sharshar T, Lefaucheur JP, Angus DC, Musthafa AA, Clermont G, Shrime MG, Ferket BS, Scott DJ, et al. Time-limited trials of intensive care for critically ill cancer patients: how long is long enough? *JAMA Oncol.* 2016;2:76-83.

159. Deeg HJ. How I treat refractory acute leukemia: a single center experience. *Blood.* 2013;121:1416-1423.

160. Schellongowski P, Staudinger T, Kundi M, et al. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with hematopoietic and acute myelogenous leukemia: a single center experience. *Haematologica.* 2011;96:231-237.

161. Enzinger AC, Zhang B, Weeks JC, PriGerson HG. Clinical trial participation as part of end-of-life cancer care: associations with medical care and quality of life near death. *J Pain Symptom Manage.* 2014;47:1078-1090.

162. Enzinger AC, Zhang B, Weeks JC, PriGerson HG. Clinical trial participation as part of end-of-life cancer care: associations with medical care and quality of life near death. *J Pain Symptom Manage.* 2014;47:1078-1090.

163. Deeg HJ. How I treat refractory acute leukemia: a single center experience. *Blood.* 2013;121:1416-1423.

164. Schellongowski P, Staudinger T, Kundi M, et al. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with hematopoietic and acute myelogenous leukemia: a single center experience. *Haematologica.* 2011;96:231-237.

165. Puxty K, McLoone P, Quasim T, KinSELLA J, Morrison D. Survival in solid cancer patients following intensive care unit admission. *Intensive Care Med.* 2014;40:1409-1428.

166. Atalatat C, Cortes J, O’Brien S, et al. Establishment of baseline toxicity expectations with standardized acute respiratory distress syndrome in acute myelogenous leukemia. *Blood.* 2007;110:3547-3551.

167. Schellongowski P, Staudinger T, Kundi M, et al. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with hematopoietic and acute myelogenous leu- kemia: a single center experience. *Haematologica.* 2011;96:231-237.

168. Cowan AJ, Altemeier WA, Johnston C, Gernsheimer T, Becker PS. Management of acute myeloid leukemia in the intensive care setting. *J Intensive Care Med.* 2015;30:375-384.

169. Hill G, Grueron 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.

170. Meert AP, Close L, Hardy M, Berghmans T, Markiewicz E, Schlemmer B, Azoulay E. The ICU strategy. A Groupe de Recherche Respiratoire En Reanimation. *Onco-Hematologique (Grr-OH) study.* *Ann Intensive Care.* 2015;5:28.

171. Lemiale V, Mokart D, Azoulay E. Non- invasive mechanical ventilation in hema- tology patients: let’s agree on several things first [serial online]. *Crit Care.* 2012;16:75.

172. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU strategy. A Groupe de Recherche Respiratoire En Reanimation. *Onco- Hematologique (Grr-OH) study.* *Ann Intensive Care.* 2015;5:28.

173. Pastores SM, Dula A, Voigt L, Raoof N, Alicea M, Halpern NA. Premortem clinical diagnoses and postmortem autopsy find- ings: discrepancies in critically ill cancer patients [serial online]. *Crit Care.* 2007;11:R48.

174. Lemiale V, Mokart D, Azoulay E. Non- invasive mechanical ventilation in hema- tology patients: let’s agree on several things first [serial online]. *Crit Care.* 2012;16:75.
196. Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect. 2012;18(suppl 7):53-67.

197. Matthes-Martin S, Feuchtinger T, Shaw PJ, et al. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECLL-4 (2011). Transpl Infect Dis. 2012;14:555-563.

198. Arendrup MC, Bille J, Dannaoui E, Ruhnke M, Heussel CP, Kibbler C. ECCL-3 classical diagnostic procedures for the diagnosis of invasive fungal diseases in patients with leukemia. Bone Marrow Transplant. 2012;47:1030-1045.

199. Skia i A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 2013;98:492-504.

200. Averbuch D, Orasch C, Cordonnier C, Zafrani L, Azoulay E. How to treat severe sepsis in patients with cancer? Critical Care of Patients With Cancer. 2012;18(suppl 7):53-67.

201. Penack O, Buchheidt D, Christopeit M, Rolston KV, Bodey GP, Safdar A. Polymicrobial sepsis and treatment of adenovirus infection in patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. Intensive Care Med. 2006;32:93-99.

202. Wohlforth P, Staudinger T, Sperr WR, et al. Prognostic factors, long-term survival, and outcome of cancer patients receiving chemotherapy in the intensive care unit. Ann Hematol. 2014;93:1629-1636.

203. Pitello N, Treon M, Jones KL, Kiel PJ. Approaches for administering chemotherapy in the intensive care unit. Curr Drug Saf. 2010;5:22-32.

204. Song JH, Suh GY, Chung MP, et al. Risk factors to predict outcome in critically ill cancer patients receiving chemotherapy in the intensive care unit. Support Care Cancer. 2011;19:491-495.

205. Schnell D, Besset S, Lengline E, et al. Impact of a recent chemotherapy on the duration and intensity of the norepinephrine support during septic shock. Shock. 2013;39:138-143.

206. 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.

207. Nazer LH, Hawari F, Al-Najjar T. Adverse drug events in critically ill patients with cancer: incidence, characteristics, and outcomes. J Pharm Pract. 2014;27:208-213.

208. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-1517.

209. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188-195.

210. 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 Care Cancer. 2002;10:425-429.

211. Reichner CA, Thompson JA, O'Brien S, Kuru T, Anderson ED. Outcome and code status of lung cancer patients admitted to the medical ICU. Chest. 2006;130:719-723.

212. Hwang JP, Patlak J, de Achaval S, Escalante CP. Survival in cancer patients after out-of-hospital cardiac arrest. Support Care Cancer. 2010;18:51-55.

213. Kazaure HS, Roman SA, Rosenthal RA, Sosa JA. Cardiac arrest among surgical patients: an analysis of incidence, patient characteristics, and outcomes in ACS-NSQIP. JAMA Surg. 2013;148:14-21.

214. Kjorstad OJ, Haugen DF. Cardiopulmonary resuscitation in palliative care cancer patients. Tidsskr Nor Laegeforen. 2013;133:417-421.

215. Reisfield GM, Wallace SK, Munsell MF, et al. Health care utilization and end-of-life care for older patients with acute myeloid leukemia. Cancer. 2015;121:2840-2848.

216. Miller SJ, Desai N, Pattison N, et al. Quality of transition to end-of-life care for cancer patients in the intensive care unit. Ann Intern Med. 2015;153:39.

217. Higginson IJ, Sen-Gupta GJ. Place of care in advanced cancer: a qualitative systematic literature review of patient preferences. J Palliat Med. 2000;3:287-300.

218. El-Jawhari AR, Abel GA, Steensma DP, et al. Health care utilization and end-of-life care for older patients with acute myeloid leukemia. Cancer. 2015;121:2840-2848.

219. Howell DA, Wang HI, Smith AG, Howard MR, Patmore RD, Roman E. Place of death in haematological malignancy: variations by disease sub-type and time from diagnosis to death [serial online]. BMC Palliat Care. 2013;12:42.

220. Bekelman JE, Halpern SD, Blankart CR, et al. Comparison of site of death, health care utilization, and hospital expenditures for patients dying with cancer in 7 developed countries. JAMA. 2016;315:272-283.

221. Goodman DC, Morden NE, Chang CH, Fisher ES, Weinberg JE. Trends in Cancer Care Near the End of Life: A Dartmouth Atlas of Health Care Brief. Hanover, NH: The Dartmouth Institute for Health Policy and Clinical Practice; 2013. dartmouthatlas.org/downloads/reports/Cancer_brief_090413.pdf. Accessed April 1, 2016.

222. Quill CM, Ratcliffe SJ, Harhoy MO, Halpern SD. Variation in decisions to forgo life-sustaining therapies in US ICUs. Chest. 2014;146:573-582.

223. Schenkner Y, Tiver GA, Hong SY, White DB. Association between physicians' beliefs and the option of comfort care for critically ill patients. Intensive Care Med. 2012;38:1607-1615.

224. Hart JL, Harhoy MO, Gabler NB, Ratcliffe SJ, Quill CM, Halpern SD. Variability among US intensive care units in managing the care of patients admitted with pre-existing limits on life-sustaining therapies. JAMA Intern Med. 2015;175:1019-1026.

225. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions,
patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA. 2008;300:1665-1673.

240. Khandelwal N, Curtis JR. Economic implications of end-of-life care in the ICU. Curr Opin Crit Care. 2014;20:656-661.

241. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. J Clin Oncol. 2010;28:1203-1208.

242. Wright AA, Zhang B, Keating NL, Weeks JC, Prigerson HG. Associations between palliative chemotherapy and adult cancer patients’ end of life care and place of death: prospective cohort study [serial online]. BMJ. 2014;348:g1219.

243. Zhang B, Nilsson ME, Prigerson HG. Factors important to patients’ quality of life at the end of life. Arch Intern Med. 2012;172:1133-1142.

244. Keating NL, Landrum MB, Rogers SO, et al. Physician factors associated with discussions about end-of-life care. Cancer. 2010;116:998-1006.

245. Scheunemann LP, Cunningham TV, Arnold RM, Buddadhumaruk P, White DB. How clinicians discuss critically ill patients’ preferences and values with surrogates: an empirical analysis. Crit Care Med. 2015;43:757-764.

246. Narang AK, Wright AA, Nicholas LH. Trends in advance care planning in patients with cancer: results from a national longitudinal survey. JAMA Oncol. 2015;1:601-608.

247. Weeks JC, Catalano PJ, Cronin A, et al. Patients’ expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367:1616-1625.

248. Matsuyama R, Reddy S, Smith TJ. Why do patients choose chemotherapy near the end of life? A review of the perspective of those facing death from cancer. J Clin Oncol. 2006;24:3490-3496.

249. Hefti PR. Necessary collusion: prognostic communication with advanced cancer patients. J Clin Oncol. 2005;23:3146-3150.

250. Azoulay E, Chaize M, Kershiff-Barnes N. Involvement of ICU families in decisions: fine-tuning the partnership [serial online]. Ann Intensive Care. 2014;4:37.

251. Voigt LP, Rajendram P, Shuman AG, et al. Characteristics and outcomes of ethics consultations in an oncologic intensive care unit. J Intensive Care Med. 2015;30:436-442.

252. Azoulay E, Timsit JF, Sprung CL, et al. Prevalence and factors of intensive care unit conflicts: the conflicus study. Am J Respir Crit Care Med. 2009;180:853-860.

253. Wright AA, Keating NL, Balboni TA, Matulonis UA, Block SD, Prigerson HG. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers’ mental health. J Clin Oncol. 2010;28:4457-4464.

254. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:1306-1316.

255. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med. 2014;2:369-379.

256. Sharma G, Freeman J, Zhang D, Goodwin JS. Trends in end-of-life ICU use among older adults with advanced lung cancer. Chest. 2008;133:72-78.

257. van Vliet M, van den Boogaard M, Donnelly JP, Evers AW, Blijlevens NM, Pickkers P. Long-term health related quality of life following intensive care during treatment for haematological malignancies [serial online]. PLoS One. 2014;9:e87779.

258. Kross EK. The importance of caregiver outcomes after critical illness. Crit Care Med. 2015;43:1149-1150.

259. Azoulay E, Pochard F, Kentsh-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171:987-994.

260. Kross EK, Engelberg RA, Gries CJ, Nielsen EL, Zatzick D, Curtis JR. ICU care associated with symptoms of depression and posttraumatic stress disorder among family members of patients who die in the ICU. Chest. 2011;139:795-801.

261. Haines KJ, Deneyel L, Skinner EH, Warrillow S, Berney S. Psychosocial outcomes and health-related quality of life of bereaved caregivers’ mental health. J Clin Oncol. 2010;28:4457-4464.

262. van Mol MM, Kompanje EJ, Benoit DD, Bakker J, Nijikamp MD. The prevalence of compassion fatigue and burnout among healthcare professionals in intensive care units: a systematic review [serial online]. PLoS One. 2015;10:e0136935.

263. Ferrand E, Lemaire F, Regnier B, et al. Discrepancies between perceptions by physicians and nursing staff of intensive care unit end-of-life decisions. Am J Respir Crit Care Med. 2003;167:1310-1315.

264. Ferrand E, Jabre P, Vincent-Genod C, et al. Circumstances of death in hospitalized patients and nurses’ perceptions: French multicenter Mort-a-l’Hôpital survey. Arch Intern Med. 2008;168:867-875.

265. Piers RD, Azoulay E, Ricou B, et al. Inappropriate care in European ICUs: confronting views from nurses and junior and senior physicians. Chest. 2014;146:267-275.

266. Quenot JP, Rigaud JP, Prin S, et al. Suffering among carers working in critical care can be reduced by an intensive communication strategy on end-of-life practices. Intensive Care Med. 2012;38:55-61.

267. Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med. 2007;356:469-478.

268. Meropol NJ, Schrag D, Smith TJ, et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. J Clin Oncol. 2009;27:3868-3874.

269. Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium—the just price. J Clin Oncol. 2013;31:3600-3604.

270. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. J Natl Cancer Inst. 2011;103:117-128.

271. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985–2000: an analysis of bed numbers, use, and costs. Crit Care Med. 2004;32:1254-1259.

272. Zafar SY, Abernethy AP. Financial toxicity, part I: a new name for a growing problem. Oncology (Williston Park, NY). 2013;27:80-81, 149.

273. Shih YC, Smieliauskas F, Neysiman DM, Kelly RJ, Smith TJ. Trends in the cost and use of targeted cancer therapies for the privately insured nonelderly: 2001 to 2011. J Clin Oncol. 2015;33:2190-2196.

274. Kongsgaard UE, Meidell NK. Mechanical ventilation in critically ill cancer patients: outcome and utilisation of resources. Support Care Cancer. 1999;7:79-99.

275. Merz TM, Schar P, Buhlmann M, Takala J, Rothen HJ. Resource use and outcome in critically ill patients with hematological malignancy: a retrospective cohort study [serial online]. Crit Care. 2008;12:R75.

276. Cheung MC, Earle CC, Rangej L, et al. Impact of aggressive management and palliative care on cancer costs in the final month of life. Cancer. 2015;121:3307-3315.

277. Zhang B, Wright AA, Huskamp HA, et al. Health care costs in the last week of life: associations with end-of-life conversations. Arch Intern Med. 2009;169:480-488.

278. Curtis JR, Engelberg RA, Bensink ME, Ramsey SD. End-of-life care in the intensive care unit: can we simultaneously increase quality and reduce costs? Am J Respir Crit Care Med. 2012;186:587-592.

279. Kulkarni AP, Divatia JV. A prospective audit of costs of intensive care in cancer patients in India. Indian J Crit Care Med. 2013;17:292-297.

280. Moors I, Benoit DD. Time to look beyond one-year mortality in critically ill hematologic patients? Crit Care. 2014;18:107.