



# Critically ill patients with cancer: chances and limitations of intensive care medicine – a narrative review

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## ABSTRACT

This narrative review deals with the challenge of defining adequate therapy goals and intensive care unit (ICU) admission criteria for critically ill patients with cancer. Several specific complications of critically ill patients with cancer require close collaborations of intensive care and cancer specialists. Intensivists require a basic understanding of the pathophysiology, diagnosis and therapy of common cancer-specific problems. Cancer specialists must be knowledgeable in preventing, detecting and treating imminent or manifest organ failures. In case of one or more organ dysfunctions, ICU admissions must be evaluated early. In order to properly define the therapy goals for critically ill patients with cancer, decision-makers must be aware of the short-term intensive care prognosis as well as the long-term oncological options and perspectives. Multidisciplinary teamwork is key when it comes down to decisions on ICU admission, planning of therapeutic aims, patient management in the ICU and tailored therapy limiting with smooth transition into a palliative care (PC) setting, whenever appropriate.

Five per cent of patients with solid tumours and up to 15% of patients with haematological malignancies require intensive care unit (ICU) admissions due to acute medical complications during the early phases of their disease.<sup>1 2</sup> In fact, every sixth to eighth European ICU patient has an underlying malignant disease.<sup>3</sup> Many of these patients present with cancer-specific complications, such as drug reactions, infectious complications after immuno/chemotherapy, expansive or infiltrative cancer growth with impairment of organ dysfunction, tumourlysis, hyperleukocytosis, need for anticancer therapy during ongoing organ dysfunction and multiple complications after stem cell transplantation. Some complications are not necessarily specific, but they occur more often in critically ill patients with cancer, such as thrombotic microangiopathies,

electrolyte disorders like hypercalcemia or the syndrome of inappropriate antidiuretic hormone secretion, and haemorrhagic and thrombotic diathesis. Finally, common ICU problems such as the acute respiratory distress syndrome or septic complications require cancer-specific diagnostic and therapeutic approaches.<sup>4 5</sup> Thus, the treatment of critically ill patients with cancer requires intensive care specialists with a solid understanding of the pathophysiology, diagnosis and therapy of common cancer-specific problems. Furthermore, haematologists/oncologists ought to be knowledgeable in preventing, detecting and treating imminent or manifest organ dysfunctions. After all, close collaboration among intensive care and cancer specialists is key in successfully managing these patients.<sup>6</sup>

## PURPOSE OF THIS REVIEW

If patients with cancer become critically ill, the following key questions are to be answered, often pressed for time: Should the respective patient be admitted to the ICU and, if so, to what extent are intensive care measures to be applied? Misjudgements at this crucial point may, at extremes, lead to lost curative therapy options or unnecessary and stressful medical treatments at the end of life. This narrative review attempts to give evidence-based assistance to address these challenges.

## DEFINING THE THERAPY GOALS FOR CRITICALLY ILL PATIENTS WITH CANCER

In general, ICU admissions are indicated if (1) the critical condition may be reversed in principal, (2) the haematological/oncological long-term prognosis and the extent of

other comorbidities justify aggressive and potentially risky therapies and (3) the respective patient does not decline intensive care treatment.

Patients and relatives, nurses and physicians of patients with cancer regularly confront themselves with questions like: will an ICU admission prolong lifetime at an acceptable quality of life, or will it extend a potentially distressful process of dying? Thus, incorporating the haematological/oncological long-term prognosis as well as the anticipated quality of life into the decision becomes pivotal. Because of the considerable heterogeneity among cancer entities and the continuous growth of effective therapeutic options, estimating the realistic expectations requires the expertise of the consulting haematologist/oncologist in many cases. Unfortunately, many institutions do not provide a round-the-clock availability of cancer specialist, even though their specific knowledge would be needed in acute cases during night and weekend times. In such situations, intensive care specialists do not only have to estimate the ICU course of the critically ill patient with cancer. They, moreover, also have to rely on proper structures and resources to prognosticate the approximate haematological/oncological long-term prognosis.

### Which factors affect the short-term prognosis of critically ill patients with cancer?

In a large investigation among European ICUs, severity of illness as well as hospital mortality was not different between patients with solid tumours and without cancer (postoperative patients included). However, in medical ICU admissions, mortality of patients with solid tumours was twice as high as in patients without cancer (41% vs 21%,  $p < 0.001$ ). On the contrary, haematological patients were sicker at ICU admission, presented with septic complications, acute respiratory distress syndrome, acute renal failure and (not surprisingly) cytopenia more often, and required vasopressors in a higher proportion. Accordingly, their hospital mortality rate was significantly higher than in all other groups of patients (58%). Finally, all patients with cancer had higher mortality rates in case of  $\geq 3$  organ failures when compared to patients without cancer (75% vs 50%).<sup>3</sup>

The occurrence of acute respiratory failure (ARF) is the most important risk factor to die for critically ill patients with cancer.<sup>7</sup> In fact, mortality is already increased in patients requiring oxygen insufflation at a rate of 1 L/min only and disproportionately increases if invasive mechanical ventilation (IMV) becomes necessary.<sup>8</sup> Mortality rates of patients with cancer and ARF undergoing IMV have dropped markedly within the past three decades. However, they still remain at  $>50\%$  in haematological patients with ARDS, and, therefore, higher than in patients without cancer.<sup>9</sup> In contrast, mortality rates of patients with cancer and severe sepsis or septic shock have not only dropped dramatically in recent years, but they also halt at rates comparable to

patients without cancer according to the reports of dedicated cancer centres.<sup>5 10</sup>

Apart from the two most common reasons for ICU admission in patients with cancer—ARF and sepsis—improved survival rates have been reported in patients admitted due to acute renal failure necessitating renal replacement therapy, neurologic complications, need for vasopressors independent of septic complications, and others.<sup>11 12</sup> Thus, no special limitations apply for the use of ICU resources in critically ill patients with cancer with curative therapeutic options or at least considerable long-term survival. Further evidence-based risk factors for critically ill patients with cancer admitted to the ICU are listed in **box 1**.<sup>13 14</sup> In general, ICU and short-term survival of critically ill patients with cancer rather depends on the degree and number of organ dysfunctions (severity of illness) than on the characteristics of the malignant disease itself.<sup>2 15</sup>

### Long-term outcomes

In patients with malignant diseases, studies on long-term survival rates as well as incidence of functional outcome variables, such as quality of life and post-ICU burden including depression, anxiety and post-traumatic stress disorder are rare. While about 15 years ago, 1-year survival rates of mixed haematological/oncological ICU cohorts ranged around 25%,<sup>16</sup> recent investigations on (mainly haematological) patients report on respective survival rates of 32–64%.<sup>17–19</sup> Many of the larger outcome studies on critically ill patients with cancer investigated mixed cohorts of haematological and

#### Box 1 Risk factors for short-term mortality of patients with cancer admitted to the ICU<sup>2 5 8 11 13 14 16 17 21 29–31 49</sup>

##### Association with increased mortality rates:

- ▶ Age,
- ▶ 'Severity of illness' (scores),
- ▶ Severity and the number of organ failures,
- ▶ Acute respiratory failure,
- ▶ invasive mechanical ventilation,
- ▶ Late intensive care unit admissions,
- ▶ Comorbidities,
- ▶ Performance Status prior to hospitalisation,
- ▶ (Very) advanced tumour stages,
- ▶ Acute graft-versus-host disease after allogeneic stem cell transplantation,
- ▶ Admission after cardiac arrest,
- ▶ Invasive pulmonary aspergillosis.

##### No association with mortality:

- ▶ Neutropenia,
- ▶ Recently administered chemotherapy,
- ▶ Autologous stem cell transplantation.

##### Association with lower mortality rates:

- ▶ Positive blood culture,
- ▶ Antibiotic combination in neutropenic sepsis (aminoglycosides?),
- ▶ Removal of central venous line in neutropenic sepsis.

oncological patients at different stages of therapy with some even including recipients of allogeneic stem cell transplantation. In general, long-term outcome of ICU survivors seems to be largely dependent on the characteristics and prognostic properties of the malignant disease, while the severity of illness during the ICU stay does seem to have any impact.<sup>2 15 16</sup> However, the evidence derived from such research is somewhat limited, and the number of studies analysing cohorts with specific malignant diseases is small.<sup>2 18 20 21</sup> Further studies on ICU cohorts with specific malignomas could further enlarge the basis for evidence-based decision-making in affected patients.

### Prognosticating short-term survival remains difficult even for specialists!

Thiery *et al*<sup>22</sup> prospectively evaluated specific ICU triage criteria in patients with cancer with  $\geq 1$  organ failure in a dedicated specialised centre (eight haematological and three oncological normal wards, 330 beds, around 130 ICU admissions of patients with cancer per year). Out of more than 200 evaluated patients, approximately every second was admitted to the ICU. The remaining patients were either categorised ‘too well’ or ‘too sick’ to be admitted to the ICU. Worrisome, 30-day mortality rate in ‘too well’ patients was 22%. On the other hand, 26% and 18% of ‘too sick’ patients were alive 30 and 180 days after the initial evaluation, respectively. The fact that in highly dedicated centres estimating an individual patient’s prognosis is far from perfect allows for speculating that in less specialised institutions the situation may even be worse.

### Possible ICU admission criteria depending on haematological/oncological prognosis

An international expert consensus has issued the following ICU admission recommendations for critically ill patients with cancer.<sup>11</sup> Even though these recommendations are based on evidence (which is mainly derived from observational trials), employing such criteria requires thorough evaluations of the applicability in individual patients.

#### 1. Full-code management

Curative ICU intention *without* primary limitations can be recommended in case of

- ▶ remission of the underlying malignancy,
- ▶ newly diagnosed malignancy with expected lifespan more than 1 year,
- ▶ availability of curative therapies, for example, in patients with haematological diseases undergoing induction or consolidation therapies,
- ▶ complications of autologous blood stem cell transplantation,
- ▶ low-grade haematological malignancies in selected patients,
- ▶ partial remission in patients with multiple myeloma,

- ▶ advanced solid cancers with therapeutic options allowing for long-term survival (more than 1 year). The increasing availability of effective anticancer therapies together with extended survival times in many cancer entities will likely contribute to an increase of patients of this group.

#### 2. ‘ICU trial’ and limiting intensive care treatment

An ‘ICU trial’, that is, an initial ‘full-code management’, followed by a re-evaluation of the goals of intensive care treatments, is indicated in patients who do not fulfil any of the above-stated criteria. This strategy applies especially to patients in whom life-extending therapies are available in principle, but whose response to therapy cannot be foreseen momentarily. In a prospective observational trial, Lecuyer *et al*<sup>23</sup> were able to show that in patients of this category (IMV with two or more organ failure) at the time of ICU admission, no clinical variable was associated with hospital mortality. The number of organ dysfunctions only *after the third day* (more pronounced even only after the fifth day) was able to differentiate between survivors and non-survivors. The mortality rate in this very ill patient cohort was 80%, while 60% of those surviving to day 3 of ICU treatment survived. Importantly, none of the patients who required an increase in intensive care treatment modalities (intubation, renal replacement therapy, vasopressors) after 3 days in the ICU survived. Thus, the individual course of such patients cannot be estimated within the first 3 days of therapy, and limiting ICU therapies should not be evaluated prior to day 3, better at day 5 of ICU treatment.

Dissenting perspectives on the adequacy of an ICU admission in individual patients among intensive care specialists and haematologists/oncologists may be solved by an ‘ICU trial’. Such decisions, even though ‘salomonic’ at first sight, should stay exceptional practice and require clinicians with sufficient knowledge of the prognosis of acute organ dysfunctions and of the malignant disease. Furthermore, it is advisable to circumvent ‘disproportionate care’ in the ICU setting, which is significantly associated with team conflicts and burnout among involved healthcare staff.<sup>24 25</sup> Ongoing evaluation of such admission practice would be of help to reveal possible targets for education and training in the context of interdisciplinary collaboration.

#### 3. No ICU admission/no intensified intensive care treatment

According to the available evidence, intensified intensive care measures—such as IMV for treatment of ARF—may not be adequate for most patients in following situations:

- ▶ no further life-extending anticancer therapies available,
- ▶ uncontrolled or refractory acute graft-versus-host disease after allogeneic stem cell transplant,
- ▶ lifespan of <1 year under ongoing anticancer therapy,

- ▶ poor performance status/bedridden over the past months,
- ▶ refusal of ICU admission by the patient.

#### 4. ICU admission outside of routine indications?

In their daily routine, intensive care specialists and haematologists/oncologists are sometimes confronted with critically ill patients who do not fit into any of the aforementioned categories. Anticipated lifespans of those patients will most likely not support unreflecting or inadequately aggressive intensive treatments. The following admission categories have been proposed for such situations but have not been evaluated in studies so far:

- ▶ ‘Exceptional ICU admissions’ in patients, in whom a poor performance status is attributable to the malignant disease itself and could be improved by anticancer therapies. This admission category applies furthermore to patients, in whom new substances may substantially extend lifespan, including enrolment in respective clinical studies.
- ▶ Further strategies include ‘prophylactic’ ICU admissions, that is, prior to the onset of acute organ dysfunctions, for example in patients with acute leukaemia or aggressive non-Hodgkin’s lymphoma, as well as ‘palliative’ ICU admissions with clear limitations concerning the invasiveness of intensive care measures. The latter approach has been evaluated in a prospective observational trial. Therein, Azoulay *et al*<sup>26</sup> analysed the outcome of patients with ARF treated with non-invasive ventilation (NIV) as ‘ceiling therapy’, meaning that NIV was performed with ‘curative’ intention. However, in case of NIV failure, patients were not intubated (do not intubate, DNI) due to unfavourable long-term prognosis, comorbidities or patient preferences. Patients with DNI had higher ICU, hospital and 90-day mortality rates (28%, 44% and 60%, respectively) compared to patients without DNI. Importantly, survivors had the same quality of life at day 90 when compared to baseline, and rates of post-traumatic stress disorder, anxiety and depression were not different between patients with and without DNI. The authors indicated that patients with cancer had higher mortality rates when compared to patients enrolled with chronic pulmonary disease or cardiac failure, but did not specify this information.
- ▶ The authors of this review do not support admitting terminally ill patients to the ICU to deliver NIV as palliative, symptom-oriented therapy, as the ICU is perceived to be associated with low quality of dying in advanced-stage cancer.<sup>27</sup> However, NIV as ‘ceiling therapy’ might be of value to some selected patients fulfilling the above-stated criteria.

#### A new and promising initiative

The British Initiative ‘Cancer patients in crisis: responding to urgent needs’ discusses the complexity of acute decision-making in case of critical events in patients with

cancer. The authors advocate for establishing a readily available information system on the characteristics of the malignant disease, medical contact persons responsible for inpatient and outpatient care, as well as regularly updated (!) patient preferences. The respective initiative provides information brochures (decision aids) for stationary and ambulatory purposes with structured emergency plans. Such tools could be helpful to determine the appropriate ‘dose’ of emergency and intensive care measures for patients with cancer in case of critical events, especially in the ambulatory environment.<sup>28</sup>

#### EARLY ICU ADMISSIONS IN CASE OF ACUTE ORGAN DYSFUNCTION!

Generally, all patients with cancer with manifest or impending organ dysfunction(s) and/or unstable vital parameters should be evaluated for ICU transfer if the above-stated criteria concerning the haematological/oncological long-term prognosis are fulfilled. All available data on critically ill patients with cancer support evaluating ICU admission *early* during their course. Even minor organ dysfunction(s) correlate with increased mortality rates, and timely transfer to the ICU seems to be associated with better outcome.<sup>8</sup> This has been specifically shown in patients with cancer and ARF and septic complications.<sup>5 8 29–31</sup>

However, the reasons for better outcomes in early transfer patients are, after all, only incompletely understood:

- ▶ While the use of *early* NIV in ARF of patients with cancer has long been advocated as standard of care, recent high-quality data question the general applicability.<sup>32 33</sup> Instead, high-flow nasal oxygen therapy has emerged as new and possibly superior therapeutic approach.<sup>34 35</sup> However, the routine administration of *any* of such methods in case of ARF in the setting of a normal ward without involvement of intensive care specialists is *not* supported by the literature.<sup>36 37</sup>
- ▶ In ICU patients with cancer and septic complications (specifically those with haematological malignancies), mortality rates have dropped dramatically around the implementation of the regularly updated Surviving Sepsis Campaign Guidelines.<sup>5 38 39</sup> It is evident that the therein-suggested bundles of care will ideally be performed in an emergency room setting or in an ICU, respectively. However, some data suggest that—even apart from sepsis or septic shock—volume management performed by intensive care specialists as means of general intensive care management may profit instable patients with cancer.<sup>37</sup>

Concerning the question ‘how early is early enough’, Lengline *et al*<sup>40</sup> presented interesting data: In a 1:1 matched analysis, the authors showed that early (prophylactic) ICU admission in high-risk patients with acute myeloid leukaemia who did not (yet) have physiologic derangements in terms of manifest organ dysfunctions was associated with increased survival rates when compared to patients who were initially managed in the



setting of a normal ward (79% vs 65%). Prospective evaluation of admission policy aiming at early prevention of organ dysfunction and, ultimately, death are urgently needed.

It has to be acknowledged, after all, that involving intensive care specialists in the care of patients at the normal ward at the threshold to organ failure may be associated with improved outcome.<sup>37</sup>

## PALLIATIVE CARE MEDICINE

The significance of PC in the context of symptom control is beyond controversy. However, reducing PC to terminal ‘end-of-life’ issues is clearly insufficient. PC depicts “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”.<sup>41</sup> Thus, the American Society of Clinical Oncology demands that “combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden,” that is, already at initial diagnosis.<sup>42</sup> This, by definition, includes patients with palliative treatment options in whom the expected lifespan may still be several years.

### Palliative care in the ICU?

Despite all recent advantages, critically ill ICU patients with cancer still bear a considerable risk of dying. Furthermore, in most instances, they experience—like patients without cancer—stressing symptoms such as thirst, anxiety, agitation, hunger, dyspnoea, pain, obstipation, sadness and confusion.<sup>43</sup> Thus, the advantages of being admitted to the ICU do not always outweigh the burden for numerous critically ill patients with cancer. Pending incongruities of wishes and beliefs may produce significant psychological strain among patients, family members, nurses and treating physicians. Family members have an increased risk for symptoms of anxiety, depression, complicated grief and post-traumatic stress disorder.<sup>44</sup>

Involving a PC team into the treatment of critically ill ICU (cancer) patients can alleviate some of the symptoms in up to 90%.<sup>45</sup> Implementation of structured communication strategies can reduce the incidence of psychiatric disorders and the need for pharmacologic treatment of ICU patients’ family members. Handing out information brochures about dying to relatives of ICU patients with high risk of dying is a particularly effective intervention.<sup>46</sup> After all, involving PC teams leads to a more reasonable use of ICU resources with shorter lengths of ICU and hospital stay, without increasing mortality.<sup>47</sup>

In the context of high mortality rates of ICU patients with cancer with  $\geq 2$  organs failure, offering PC

structures *parallel* to curative ICU efforts is, therefore, not an option, but an *obligation*. The multidisciplinary project ‘Improving Palliative Care in the ICU’ propagates implementing a simple but evidence-based bundle of PC measures and offers a profound information resource for patients, families, intensive care and PC teams.<sup>48</sup>

## CONCLUSION

Correct estimation of the ICU (short-term) as well as haematological/oncological (long-term) prognosis is an essential when setting the goals of therapy in critically ill patients with cancer. Excellent cooperation between haematologists/oncologists and intensive care specialists is, therefore, of utmost interest. The available evidence-based consensus of an international expert team on possible ICU admission criteria offers a solid base for decisions. For many patients with cancer, ‘full-code management’ without limitations of ICU resources can be considered state of the art. The available evidence suggests that patients with cancer profit from early ICU admission, maybe even prior to the onset of organ dysfunctions in high-risk patients. Limiting therapies in patients admitted for an ‘ICU trial’ should not be performed before the evolution of the patient has been monitored for several (ideally  $\geq 5$ ) days, because the prognosis cannot be estimated until then. First data suggest that admitting carefully selected patients with cancer to the ICU with clear and upfront limits of therapy may be justifiable. Admitting patients with cancer to the ICU for the mere administration of end-of-life therapies is not established. However, implementing PC concepts as parallel structure to curative ICU therapies should nowadays be one of the basic principles in modern intensive care management of (not only) patients with cancer.

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