

Outcome in Critically Ill Cancer Patients: Past and Present*

Prognóstico de Pacientes com Câncer Criticamente Enfermos: Passado e Presente

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RESUMO

JUSTIFICATIVA E OBJETIVOS: Até o final do século passado, havia grande incerteza quanto a propriedade de internar pacientes com câncer em unidades de terapia intensiva (UTI) para medidas de suporte avançado. Contudo, ao longo dos últimos anos, vários centros ao redor do mundo têm reportado aumento significativo da sobrevivência de tais pacientes. O objetivo deste estudo foi rever os principais artigos publicados nas duas últimas décadas, com foco na melhoria do prognóstico de pacientes com câncer criticamente enfermos.

CONTEÚDO: Realizou-se uma busca bibliográfica no sistema MedLine – PubMed (www.pubmed.gov) para identificar artigos em linguagem inglesa sobre cuidados intensivos no pacientes com tumores sólidos ou neoplasias hematológicas, com ênfase no prognóstico e no tratamento. Utilizaram-se os seguintes unitermos: *cancer, solid tumor, hematologic or hematological malignancies, immunosuppression, ICU, ventilation, organ failure, sepsis and infection*. Estudos referenciados nos artigos selecionados na busca também foram utilizados.

CONCLUSÕES: O tema será abordado de forma sistematizada. Inicialmente, haverá uma discussão sobre o prognóstico sombrio experimentado por estes pa-

cientes no passado. Subseqüentemente, serão discutidos os estudos publicados nos anos recentes sobre a melhoria do prognóstico para os diversos subgrupos de pacientes, a despeito de uma maior gravidade das complicações agudas. Para finalizar, será discutido o papel da ventilação não-invasiva como estratégia inicial de ventilação para estes pacientes.

Unitermos: câncer, prognóstico, Medicina intensiva, ventilação artificial.

SUMMARY

BACKGROUND AND OBJECTIVES: Until the end of the previous century it remained controversial to admit cancer patients to the ICU for advanced-life-supporting therapy. However, over the past few years several centres over the world have shown that it is possible to achieve a meaningful survival in these patients. The aim of this review is to focus on the improvement in outcome that has been achieved over the past two decades in critically ill cancer patients.

CONTENTS: We performed a MEDLINE search (period of 1980 to November 2007) to identify full-text English language publications on critically ill patients with solid tumors or hematological malignancies with particular interest for the outcome and treatment. Major MESH search terms included; cancer, solid tumor, hematologic or hematological malignancies, immunosuppression, ICU, ventilation, organ failure, sepsis and infection. Additional studies were identified through a manual search of citations from retrieved articles.

CONCLUSIONS: In this review, we first focus on the grim prognosis in the past, subsequently we discuss the improvements in outcome over the past few years across subgroups of cancer patients with increasing degree of severity of illness, and finally, we focus on the value of non-invasive ventilation since it is considered the initial ventilatory strategy in these patients.

Key Words: cancer, intensive care, mechanical ventilation, outcome

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INTRODUCTION

The long-term survival of patients with hematological malignancies has substantially improved over the past two decades. Nowadays, approximately 40% of the patients with high-grade malignancies such as acute myelogenous leukemia or non-Hodgkin lymphoma survive for more than 5 years and it is estimated that nearly 30% of these patients can be cured¹. Although low-grade hematological malignancies remain incurable, half of the patients will survive for more than 4 years and survival for more than 8 to 10 years is not exceptional in diseases such as chronic lymphocytic leukemia or multiple myeloma. Similar improvements in prognosis can be observed in several solid cancers such as in tumors of the breast, head and neck region and the lower gastro-intestinal tract¹. These advances in outcome have been achieved by earlier detection, particularly in solid tumors, by a better risk stratification of patients due to advances in radiology, immuno-histology and cytogenetics, by the use of new or intensive chemotherapeutic regimens with or without bone marrow or peripheral stem cell rescue and by advances in supportive care. As a drawback however, the therapeutic intensification coupled with longer survival time has led to an increased occurrence of potential life-threatening complications requiring ICU admission in these immunosuppressed patients^{2,3}.

OUTCOME IN CRITICALLY ILL CANCER PATIENTS: EVOLUTION OVER THE PAST TWO DECADES

Despite the substantial improvement in long-term outcome and quality of life that has been observed in cancer patients over the past two decades, now equalling those of non-cancer chronic illness patient populations^{4,5}, it remained however, controversial whether severely ill cancer patients should be admitted to the ICU for advanced life-supporting therapy until the end of previous century^{6,7}. The high mortality of more than 80% in patients requiring mechanical ventilation (Table 1)⁸⁻¹⁵, increasing to more than 90% to 95% in patients developing multiple organ failure or who require renal replacement therapy during ICU stay^{12,16-18}, particularly in the transplant setting¹⁹⁻²¹, together with the severe emotional burden endured by these patients and their relatives, and the considerable costs of advanced and prolonged life-supporting therapy¹³ resulted in a general reluctance to admit such patients to the ICU^{2,6,7}. However, over the past few years, several centres throughout the world have been reporting on increasingly improving survival in critically ill patients with hematological malignancies and solid tumors²²⁻³¹, approaching survival rates reported in general ICU patients³². In a case-historical control study²², Azoulay et al. reported a four-fold lower risk of death in cancer patients who required mechanical ventilation between 1996 and 1998 as compared with 1990-1995. Although the severity of illness upon ICU admission significantly increa-

Table 1 – Hospital Mortality in Ventilated Cancer Patients; Evolution Over the Past Two Decades^a

Authors	Patients (n)	Solid Tumours (n)	Hematologic Malignancies (n)	Mortality (%)
Schuster and Marion ⁸ , 1983	52	0	52	92
Ewer et al. ⁹ , 1986	46	46	0	91
Peters et al. ¹⁰ , 1988	116	0	116	82
Brunet ¹² , 1990	111	0	111	85
Sculier and Markiewicz ¹¹ , 1991	64	37	27	80 / 70
Shapira et al. ¹³ , 1993	54	24	30	75 / 76
Epner et al. ¹⁴ , 1996	86	0	86	75
Groeger et al. ¹⁵ , 1999	782	305	404	63 / 84
Kress ²⁴ , 1999	153	95	58	67 ^b
Azoulay et al. ²² , 2001	237	68	169	76 / 71 ^c
Massion et al. ²⁶ , 2002	48	0	48	75
Benoit et al. ²⁸ , 2003	88	0	88	68
Maschmeyer et al. ²⁷ , 2003	189	103	86	73 ^b
Depuydt et al. ²⁹ , 2004	166	0	166	71
Azoulay et al. ³⁰ , 2004	203	23	180	75 ^b
Soares et al. ³¹ , 2005	463	359	104	65 / 68

^aLimited to the most important studies which did not focus exclusively on bone marrow or peripheral stem cell transplant recipients. ^bSubgroup mortality rates are not reported. ^c30 days mortality rates

sed between these two periods, the hospital mortality decreased from 82% to 61% ($p < 0.001$). This was also confirmed in cancer patients with septic shock²³. The same conclusion can be drawn when focusing on crude mortality rates reported over the past 2 decades in the more severe ill subgroups such as those requiring mechanical ventilation (Table 1), renal replacement therapy or both³³⁻³⁵. While most centres reported a mortality of 85%-90% in ventilated cancer patients until the end of previous century, most report a mortality of 65%-70% today. In a recent large prospective study including 463 cancer patients who were ventilated > 24 hours, Soares et al.³¹ reported a hospital mortality of 64%. Recommendations regarding the duration of mechanical ventilation have also changed over the past 2 decades. Until the end of 1980, most authors recommended to ventilated cancer patients for no longer than 5-7 days because of 100% mortality^{8,9}. However, the duration of mechanical ventilation is no longer reported to be of prognostic importance today^{22,29-31}. For instance, of the 112 patients with hematological malignancies ventilated in our centre > 7 days between 1997 and 2007, 26% survived to hospital discharge and 20% were still alive at 6 months (unpublished data). However, the survival of ventilated allogeneic bone marrow or peripheral stem cell transplantation recipients remains particularly poor¹⁹⁻²¹ although some improvement has been achieved³⁶⁻³⁸. Encouraging results have also been obtained in cancer patients requiring renal replacement therapy for acute renal failure, even in case of multiple organ failure or in combination with ventilatory support³³⁻³⁶. While renal replacement therapy was unequivocally associated with a 90-95% ICU mortality in case of multiple organ failure two decades ago^{12,18}, Soares et al.³¹ recently reported 65% six month mortality in patients with one or two associated organ failures and a 93% six month mortality in case of 3 associated organ failures, again similar to general ICU patients³². Moreover, in a study by Benoit et al. comparing the six-month survival between critically ill patients with and without hematological malignancy, the presence of an underlying hematological malignancy was not independently related with six-month survival once accounting for the severity of illness upon ICU admission or the duration of hospitalization prior to admission³³. Finally, recently two centres reported the survival rates of cancer patients who underwent urgent chemotherapy while being critically ill^{39,40}. Although clearly, these patients were highly selected, meaningful long-term survival was observed despite the need for advanced life-supporting therapy

during ICU stay in patients with hematological malignancies or chemo-sensitive solid tumors at first presentation of their disease, a finding that no one could have been thought of being possible a few years ago.

These improvements in outcome can be attributed to a better selection of patients with respect to their underlying malignancy and subsequent expected long-term prognosis^{22,28,31,40}, the increasing use of peripheral blood stem cell transplantation³⁶, the availability of better supportive measures in the subgroup of immunocompromised patients such as of non-invasive ventilation^{22,41} and last but not least the advances in the treatment of sepsis and in ICU support in general^{42,43}.

PROGNOSTIC INDICATORS: SUBGROUPS WITH A BETTER AND WORSE OUTCOME

It is clear from the previous data that the presence of an underlying cancer alone can no longer be considered a contra-indication to refer or admit patients to the ICU, even for advanced life-supporting therapy. However, these relative good results should neither be used to justify therapeutic perseverance nor to withhold palliative care in patients who are in a desperate situation. Providing advanced life-supporting therapy to patients with a dismal chance of successful recovery, regardless of whether it is related to an underlying cancer or other severe co-morbidity, is associated with a huge emotional burden for patients, relatives and caregivers as well, and is associated with considerable cost for the society¹³. However, the decision to provide or withhold advanced life-supporting therapy remains difficult in an individual patient in daily practice. The complexity of such a decision cannot be replaced by a simple number of prognostic indicators, by a rule of thumb or even by a more complex scoring system^{44,45}. Even ICU physicians often dealing with such patients fail to discriminate well between survivors and non-survivors⁴⁶. Nevertheless, a number of prognostic indicators have been identified to guide physicians in their decision-making^{15,16,27-31,44}. Of course beside these prognostic indicators, the patient's perceived quality of life and the wishes of the patient and/or the relatives should also be taken into account. Advanced care planning and good and honest communication regarding the patient's prognosis between the patient and/or relatives, the attending hemato-oncologist and the ICU physicians upon referral to the ICU is therefore essential. In case of doubt a 3 days therapeutic trial can be tried⁴⁷. As in every patient who is referred to the ICU, the de-

gree and duration of advanced life-supporting therapy should be in proportion with the expected long-term survival. Of course, the type of cancer and its available treatments, the cancer status and the remaining therapeutic options in case of relapse or active disease are important to take into account. Age has only a minimal impact on the six-month survival in critically cancer patients⁴⁸. The performance status and comorbidity are much more important^{44,49,50} for both the long-term and the short-term survival. The short-term survival, however, will essentially depend upon the number and severity of organ failures and the subsequent need for advanced life-supporting measures such as mechanical ventilation and/or renal replacement therapy on the one hand^{16, 28-35}, and the reversibility of the organ failure on the other^{17,51}. The latter will essentially depend upon the availability of an effective treatment and the time until response to such treatment. Paradoxically, bacterial infection has been found to be associated with a better outcome in several studies, particularly in patients with hematological malignancies and this regardless of the degree of advanced life-supporting therapy^{26,28,29,33,41,43,52,53}. It is a serious complication, which is associated with an average mortality of 30% in patients without pulmonary infiltrates^{43,53}, increasing to 65% in patients with pulmonary infiltrates^{43,53,54} or who require ventilatory support^{28,29,43,53} and up to 75% in those with multiple organ failure^{33,53}, regardless of the microbiological documentation^{43,53}. However, it is at least a treatable and potentially more rapidly reversible complication^{28,29,33,43,53} compared to many other complications in cancer patients such as major organ involvement by solid tumor^{31,49} or hematological malignancy^{40,55}, invasive pulmonary aspergillosis^{28-30,33,43,52,53}, post-transplant related complications^{38,56}, or an uncertain diagnosis^{30,41,43,53}. In a study by Benoit et al.⁵³, patient with hematological malignancies requiring mechanical ventilation because of a documented or clinically suspected bacterial infection had a hospital mortality of 65% compared to 85% in those ventilated for other reasons ($p < 0.001$). In another study by the same group in patients requiring renal replacement therapy in combination with ventilatory support for the majority, the mortality in patients with bacterial infection was 74% compared to 95% in those without ($p = 0.059$)³³. Important to note is that the mortality rates in these subgroups of patients are similar to the general ICU patients with severe infection⁵⁷ regardless of the recent administration of chemotherapy⁴³.

NONINVASIVE OR INVASIVE MECHANICAL VENTILATION?

Acute respiratory failure is common in critically ill cancer patients, and often necessitates mechanical ventilatory support while the underlying cause is searched for and, if possible, treated^{29,30}. Hypoxemic respiratory failure may be due to infectious pneumonia^{26,28-31,52,53}, invasion of the underlying malignancy^{39,45,51,55}, chemotherapy-related acute lung injury⁵⁶, cardiogenic and noncardiogenic pulmonary edema²⁸⁻³⁰ or diffuse alveolar bleeding⁵⁶, whereas hypercapnic respiratory failure may result from comorbidity such as COPD. Noninvasive mechanical ventilation (NIV) is firmly established as first line treatment in hypercapnic patients⁵⁸. As well, two small randomized controlled trials, one in immunocompromized patients and the other in solid organ recipients, favored NIV over invasive ventilation in hypoxemic respiratory failure, with a very high mortality in the invasively ventilated arm^{41,59}. However, NIV should be used with some caution in hypoxemic cancer patients. It should be kept in mind that the results of NIV in hypoxemic respiratory failure in non-immunocompromized patients without cardiogenic pulmonary edema are conflicting⁶⁰. For example, a recent meta-analysis of the use of NIV in patients with acute respiratory distress syndrome found no benefit associated with NIV⁶¹. Whereas the cause of hypercapnic respiratory failure is essentially pump failure, mainly due to COPD, the causes of intrinsic lung failure leading to hypoxemic respiratory failure are far more heterogeneous: the success of a NIV trial depends upon the underlying cause, which should be treatable and rapidly reversible. As we discussed above, mortality of acute hypoxemic respiratory failure in hematological patients relates not only to the choice of mechanical ventilation, but to the underlying diagnosis as well^{29,30,41}. In the aforementioned study by Hilbert et al.⁴¹, more patients in the NIV arm had a diagnosis of infectious pneumonia, a potentially reversible condition, and this may in part have biased towards the good outcome in NIV-treated patients. A further caveat to the indiscriminate use of NIV in hypoxemic patients is the high mortality of more than 90% associated with NIV failure, as observed by Azoulay and Depuydt^{29,30}. In conclusion, a judicious trial of NIV should be offered to selected, hemodynamically stable and cooperative hematological patients, especially when the cause of hypoxemia appears to be rapidly reversible. However, patients need to be monitored closely for predictors of NIV failure, such as increasing hypoxemia or acidosis⁶².

CONCLUSIONS

Until the end of previous century it remained controversial to refer or admit cancer patients to the ICU. However, over the past decade, several centres over the world have shown that it is possible to achieve meaningful outcome in these patients. These relatively good results should, however, not be used to justify therapeutic perseverance or to postpone palliative care in patients who are in a desperate situation. Similarly to any other critically ill patient, the degree and duration of advanced life-supporting therapy provided should be in proportion to the patient's expected long-term survival and quality of life. Honest communication regarding these issues between the caregivers, the patient and the relatives before and upon referral to the ICU as well as during ICU stay is therefore essential.

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