Clinical characteristics and outcomes of critically ill cancer patients with septic shock

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Summary

Objective: To evaluate the clinical characteristics and outcomes of critically ill cancer patients with septic shock.

Design: Prospective, observational cohort study.

Methods: Medical–surgical intensive care unit (ICU) at the Instituto Nacional de Cancerología located in Mexico City from January 2008 to February 2010. There were no interventions. Eighty-two consecutive cancer patients with septic shock aged over 18 years were prospectively included and evaluated.

Results: During the study period, 620 critically ill cancer patients were admitted to ICU. Ninety-four patients were evaluated for septic shock at the request of ward onco-hematologists or surgeon oncologist responsible for the patient. After being evaluated by the intensivists, 82 patients were admitted to the ICU. Of the 82 patients, 56 (68.3%) had solid tumours and 26 (31.7%) had hematological malignancy. The most frequent sites of infection were: abdominal (57.3%) and respiratory (35.8%). Cultures were positive in 41 (50%) patients. The 63.4% of the patients had three or more organ dysfunctions on the day of their admission to the ICU. Cox multivariate analysis identified the Sequential Organ Failure Assessment (SOFA) score [hazard ratio (HR): 1.11; 95% confidence interval (95% CI): 1.02–1.19, \( P = 0.008 \)] and performance status (PS) ≥ 2 (HR: 1.84; 95% CI: 1.03–3.29, \( P = 0.040 \)) as independent predictors of death to 3 months. The ICU mortality rate was 41.5% (95% CI: 31–52%).

Conclusion: The variables associated with increased mortality were the degree of organ dysfunction determined by SOFA score at ICU admission and PS ≥ 2.

Introduction

The treatment of septic shock is a complex process and a significant challenge to intensivists. Septic shock is defined as severe sepsis with a state of acute circulatory failure characterized by arterial hypotension despite adequate fluid resuscitation, so that vasopressor therapy is necessary to restore a minimally acceptable arterial pressure and is associated with a high mortality rate. Cancer patients have a greater tendency to acquire infections than non-cancer patients. Severe sepsis is a common complication in cancer patients with an estimated 16.4 cases per 1000 persons living with cancer. Annane et al. studied the epidemiology of septic shock in Paris and its suburbs and reported that the 15.3% had cancer or hematologic malignancy.
A similar proportion (16.9%) was observed in two large studies. A few studies have been published specifically centered on septic shock and its prognosis in cancer patients. Septic shock among cancer patients has overall mortality rates ranging from 53.4% to 65.5%. Recently, Péne et al. reported the outcomes in cancer patients with septic shock over two consecutive 4-year periods: 1998–2001 and 2001–2005. In their study, they found that mortality of cancer patients hospitalized in the ICU with septic shock decreased over time. Patients of the period 2001–2005 were more likely to be alive at Day 28 (47.3 vs. 27.8%). This reduction in mortality rate could be explained by the better selection of patients and improvements in the care and management, including new therapeutic strategies for sepsis.

On this basis, we conducted this study with the aim of evaluating the clinical characteristics and outcomes of critically ill cancer patients with septic shock admitted to an oncological intensive care unit (ICU).

Materials and methods

Design and setting

Prospective, observational cohort study was performed at the Instituto Nacional de Cancerología (INCan) located in Mexico City, from January 2008 to February 2010. The medical–surgical ICU has six beds, with medical and nursing staff that are qualified in intensive care. Data on the characteristics and organization of the ICU have been previously reported. The present study was observational and descriptive. The Bioethics Committee of the INCan approved this study and the need for informed consent was waived.

Selection of participants, data collection and definitions

During the study period, all consecutive patients aged over 18 years with solid tumor or hematologic malignancy and treated for septic shock in our ICU were prospectively included and evaluated. The readmissions were not considered, only the first episode of septic shock was analyzed. ICU admission is considered when a cancer patient has at least one organ failure and preferably with the lowest SOFA score before admission to ICU, remission/stable disease or the prognosis is unclear or not yet assessable. Patients are not admitted to our ICU when they refuse ICU admission. Decisions to admit a patient to the ICU are usually considered together by the intensivist and the onco-hematologists or surgeon oncologist responsible for the patient. Demographic, clinical, and laboratory data were collected during the first day of ICU stay including hospital location before ICU admission, performance status (PS) (Eastern Cooperative Oncology Group scale) during the last month before hospitalization, type of tumor, cancer status, tumor stage, cancer- and treatment-related data, need for mechanical ventilation (MV), length of MV, type of pathogens in positive cultures, source of infection and ICU mortality rate. The Eastern Cooperative Oncology Group scale was used to divide the patients into two groups: 0–1 and ≥2. The length of stay in the ICU was measured as the number of days from admission to the ICU until discharge from the ICU. Acute physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score were calculated on the first 24 h after admission to the ICU. Septic shock was defined by persistent arterial hypotension unexplained by other causes. Hypotension was defined by a systolic arterial pressure below 90 mmHg, a mean arterial blood pressure <60, or a reduction in systolic blood pressure of 40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes. Neutropenia was defined as white blood cells count <1000 leukocytes/mm3. Malignancies were grouped as: hematologic malignancy and solid tumors. Clinical stages were categorized into I/II and III/IV. The treatment intention was categorized into three categories: curative treatment, adjuvant treatment and palliative treatment. All patients were treated following the guidelines for management of severe sepsis and septic shock. Patients were empirically treated with intravenous antibiotic therapy as early as possible and within the first hour of recognition of septic shock depending on the site of infection, known colonization with resistant pathogens, and previous antibiotic treatment. Appropriate antifungal or antiviral drugs were added according to clinical suspect. De-escalation to the most appropriate single therapy was performed as soon as the susceptibility profile was known. In addition, source control measures, such as surgery or device removal, were applied if necessary. In our ICU clinical rounds with an infectious disease specialist are carried out every day.

Data presentation and statistical analyses

Continuous variables are expressed as means ± SD, or as medians and interquartile ranges (IQRs), if the distribution was skewed. Categorical variables are expressed as percentage. Student’s t-test or the Mann–Whitney U-test were used to compare continuous variables according to the data distribution.
normal or non-normal, respectively, determined using the Kolmogorov–Smirnov test), and the chi-squared or Fisher’s exact test was used to compare categorical variables.

Cox proportional hazards univariate and multivariate analysis were used to identify factors with potential prognostic significance with 3-month survival. Variables selected in the univariate analysis ($P<0.25$) and those considered clinically relevant were included in a multivariable Cox proportional hazards regression model to estimate the independent contribution of each variable on the mortality. Results were reported using hazard ratios (HRs) and corresponding 95% confidence interval (95% CI). Survival time was defined as the time (days) from the ICU admission to death from any cause up to 3 months of follow-up. Survival curves were estimated using the Kaplan–Meier method. The log-rank test was used to compare overall survival data. A two-sided $P$-value $<0.05$ was used to determine statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences software (version 15.0; SPSS, Chicago, IL, USA).

**Results**

During the study period, 620 critically ill cancer patients were admitted to ICU. Ninety-four patients were evaluated for septic shock at the request of ward onco-hematologists or surgeon oncologist responsible for the patient. After being evaluated by the intensivist, 82 patients were admitted to the ICU (Figure 1). Of the 12 patients who were not admitted, 9 patients were considered too sick to benefit from intensive care, and 3 patients refused admission to ICU. Descriptive characteristics for this cohort are presented in Table 1. The main sources of admission were the operating room (42/51.2%), ward/floor (37/45.1%) and another area of the hospital (3/3.7%). Of the 82 patients, 56 (68.3%) had solid tumors and 26 (31.7%) had hematological malignancy. The hematologic malignancies were non-Hodgkin’s lymphoma ($n=13$; 50%), acute lymphoid leukemia ($n=8$; 30.8%), acute myeloid leukemia ($n=2$; 7.7%), chronic myeloid leukemia ($n=2$; 7.7%) and myelodysplastic syndrome ($n=1$; 3.8%). Tumor and non-Hodgkin’s lymphoma stages are presented in Table 2. In terms of cancer status, 58.5% had a recurrence or progression, 34.1% were newly diagnosed, 6.1% had complete remission of disease and 1.2% had no response to treatment. Previous treatments included chemotherapy ($n=44$; 53.7%), surgery ($n=35$; 42.7%) and radiotherapy ($n=25$; 30.5%). Twenty-six patients (31.7%) received curative treatment, 18 patients (22%) received adjuvant treatment and 38 (46.3%) received palliative treatment. Sources of infection were: abdominal (57.3%), respiratory (35.8%), urinary (3.6%) and skin and soft tissue (1.2%). Seven (9.7%) patients had neutropenia. Cultures were positive in 41 (50%) patients with predominance Gram-negative bacilli. The microorganisms are presented in Table 3. The incidence of organ dysfunction was noted to be more frequent for the respiratory, cardiovascular, coagulation and renal systems (100, 100, 51.2 and 45.1% of cases, respectively). The 63.4% of the patients had three or more organ dysfunctions on the day of their admission to the ICU. Table 4 lists the results of Cox proportional hazards univariate analysis of factors associated with increased 3-months mortality rate. Cox multivariate analysis identified the SOFA score (HR: 1.11; 95% CI: 1.02–1.19, $P=0.008$) and PS $\geq 2$ (HR: 1.84; 95% CI: 1.03–3.29, $P=0.040$) as independent predictors of death to 3 months (Table 5). The ICU mortality rate was 41.5% (95% CI: 31–52%) (Figure 1). The ICU
survival by SOFA score is depicted in Figure 2, indicating that the patients having a SOFA score higher than 10 at admission to ICU had less possibility to not survive the ICU stay.

**Discussion**

Cancer patients are at greater risk for severe sepsis than the general population, probably related to immunosuppression caused by the malignancy itself or its treatment. The incidence of severe sepsis is four times higher in cancer vs. non-cancer patients. The ICU mortality rate for cancer patients with septic shock in our study is lower than that previously reported. The progressive reduction in mortality rates for septic shock is related to improved supportive care, protocolized systems for the rapid and appropriate use of treatment interventions, and prevention of complications. The guidelines for management of severe sepsis and septic shock are applicable to patients who have cancer. Recently, Penê and colleagues reported decrease in mortality of critically ill cancer patients with septic shock. This was associated with significant implementation of treatment guidelines derived from positive interventional trials in septic shock. In our ICU all patients are treated following the guidelines for management of severe sepsis and septic shock.

The most frequent sites of infection in cancer patients are: respiratory (35.4–49.1%), abdominal (18.5%) and urinary tract (16%) with predominance (65%) of Gram-negative bacilli. The source of infection is associated with the type of malignancy, patients with prostate cancer had the highest rate of urinary tract infections leading to sepsis, at 48%, and patients with a history of gastrointestinal malignancy were most likely to acquire intra-abdominal sepsis (36%). In this study, the most common source of infection were abdominal with predominance Gram-negative bacilli, this could be related with underlying malignancies because the most of patients had gynecological and gastrointestinal malignancy and they were admitted to ICU after of surgical procedure.

Soares et al. studied the effect of age on survival of critically ill patients with cancer, they reported that aging was associated with increased mortality, especially for patients >60 years. In our study, age was not an independent predictor of a worse prognosis as has been reported in other studies. However, in these studies, the assessment of the effect of age was limited by low number of patients.

**Table 1** Clinical characteristics of patients on admission to the ICU

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors, n = 48</th>
<th>Non-survivors, n = 34</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.13 ± 13.87</td>
<td>51.65 ± 15.86</td>
<td>0.656</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>30 (62.5)</td>
<td>21 (61.7)</td>
<td>0.946</td>
</tr>
<tr>
<td>SOFA score</td>
<td>9.1 ± 3</td>
<td>11.7 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>15 (13–19.5)</td>
<td>18 (16–23)</td>
<td>0.009</td>
</tr>
<tr>
<td>Length of MV (days)</td>
<td>7.5 (3–16.5)</td>
<td>3 (2–9)</td>
<td>0.014</td>
</tr>
<tr>
<td>PEEP (cmH2O)</td>
<td>5 (5–8)</td>
<td>7 (6–10)</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of vasopressors (days)</td>
<td>6.5 (3–12.5)</td>
<td>3 (2–9)</td>
<td>0.024</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>10 (6–17.5)</td>
<td>3 (2–8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total bilirubin (µmol/l)</td>
<td>13.6 (10.2–24.8)</td>
<td>17.1 (11.9–39.3)</td>
<td>0.138</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>77.8 (53–128.2)</td>
<td>106.1 (61.9–247.5)</td>
<td>0.034</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>6.52 (5.58–9.1)</td>
<td>5.85 (5.32–8.82)</td>
<td>0.207</td>
</tr>
<tr>
<td>Leukocytes (x10^9/l)</td>
<td>9.5 (4.9–17.1)</td>
<td>5.8 (2.4–8.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>100 ± 20.4</td>
<td>99.2 ± 34.3</td>
<td>0.897</td>
</tr>
<tr>
<td>Platelets (10^9/l)</td>
<td>206.8 ± 159.8</td>
<td>134.6 ± 133.9</td>
<td>0.035</td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumor, n (%)</td>
<td>34 (70.8)</td>
<td>22 (64.7)</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy, n (%)</td>
<td>14 (29.2)</td>
<td>12 (35.3)</td>
<td></td>
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<tr>
<td>Tumor stage (n = 69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II, n (%)</td>
<td>14 (32.5)</td>
<td>10 (38.5)</td>
<td></td>
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<tr>
<td>III/IV, n (%)</td>
<td>29 (67.5)</td>
<td>16 (61.5)</td>
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<td>PS, n (%)</td>
<td></td>
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<tr>
<td>0–1</td>
<td>35 (72.9)</td>
<td>25 (73.6)</td>
<td>0.951</td>
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<tr>
<td>≥ 2</td>
<td>13 (27.1)</td>
<td>9 (26.4)</td>
<td></td>
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</tbody>
</table>

PEEP: positive end-expiratory pressure.
In the present study, the independent variables associated with increased mortality were the degree of organ dysfunction determined by SOFA score at ICU admission and PS $\geq 2$. One of the
The outcomes of critically ill patients with cancer are dependent mainly of the nature and the degree of organ dysfunction, poor PS, and comorbid illnesses. PS is used by oncologists, hematologist, surgical oncologists and researchers to establish the extent of a patient’s disability. It is a very useful tool in oncology and it is important to determine appropriate treatment and prognosis. Poor PS is associated with increased mortality in critically ill cancer patients; however, previous studies focused specifically on critically ill cancer patients with septic shock did not report specific information about PS before admission to ICU. In our study, patients with PS ≥ 2 during the last month before hospitalization had marked clinical deterioration as a result of the underlying disease.

The outcome of critically ill cancer patients admitted to ICU is not homogeneous; solid tumors have a lesser impact on mortality than hematological cancers, however, in accordance with previous reports, in this study the type of malignancies and clinical stage was not associated with a poorer outcome; however, the low number of patients might have limited this result.

The present study has some limitations in that we had no specific information about histological findings, represents the experience of a single oncological ICU and the sample size is relatively small, which might influence the statistical power as well as limit the generalization of its findings.

**Conclusion**

The present study shows that survival in cancer patients with septic shock admitted to the ICU has been improved and confirming the current trend toward a decrease in the mortality of cancer patients. The variables associated with increased mortality were the degree of organ dysfunction determined by SOFA score at ICU admission and PS ≥ 2.

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References


