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Original Paper

Prognostic Factors for Neutropenic Patients in an Intensive Care Unit: Respective Roles of Underlying Malignancies and Acute Organ Failures

F. Blot,[1] M. Guiguet,[2] G. Nitenberg,[1] B. Leclercq,[1] B. Gachot[1] and B. Escudier[1]

[1]Intensive Care Unit, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif; and [2]INSERM U 444, Hôpital Saint Antoine, Paris, France

The admission of neutropenic patients to an intensive care unit (ICU) is still controversial, especially if mechanical ventilation is required. To avoid useless stays in ICU, the evaluation of the respective role of the underlying malignancy and acute organ failures might be useful for better definition of the categories of patients who could benefit from aggressive ICU support. For this purpose, we carried out a retrospective study of the charts of 107 consecutive neutropenic patients admitted to an ICU in a comprehensive cancer centre over a four-year period. The following characteristics were recorded within 24 h of admission: patient data, characteristics of neutropenia and the underlying malignancy, the type and number of organ system failures (OSFs) and simplified acute physiological scores (SAPS and SAPS II). The impact of each variable on outcome in the ICU was studied by univariate and multivariate (logistic regression) analysis. 59 patients died in the ICU (mortality rate: 55%). Patients with a haematological malignancy ($n = 57$, 53%) were more likely to experience respiratory failure, an underlying malignancy deemed rapidly fatal, and to have longer lasting neutropenia than patients with a solid tumour ($n = 50$, 47%). However, the mortality rate did not differ in the two groups (haematological malignancy 61% versus solid tumour 48%, $p = 0.16$). Respiratory and cardiovascular organ failure ($p < 0.001$ for both) correlated with mortality in the ICU. In the multiple logistic regression model, only the number of organ system failures and respiratory failure remained predictive of ICU mortality. In conclusion, the characteristics of the underlying malignancy are not relevant when deciding whether or not neutropenic patients should be admitted to an ICU. The main risk factors for death in an ICU are the number of organ failures on admission, and among them the presence of respiratory failure. © **1997 Elsevier Science Ltd.**

Key words: cancer, neutropenia, intensive care, respiratory failure, prognosis

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INTRODUCTION

BECAUSE THE results of conventional chemotherapy in oncology have been disappointing, there is currently a trend towards the development of more aggressive regimens. However, despite the use of haematological growth factors, these regimens predispose patients to various life-threatening complications, such as infection, haemorrhage or drug-related toxicity [1–14]. Owing to the need for continuous monitoring or aggressive support, some of these complications may require transfer to an intensive care unit (ICU). However, given the very high mortality rates recorded for neutropenic patients admitted to ICUs, especially when mechanical ventilation is required [2–4, 6, 7, 10, 11], it is essential to identify the categories of patients most likely to benefit from ICU support. In this regard, the respective effects of the underlying malignancy and acute organ failures on the outcome of neutropenic patients have not yet been clearly defined. Such clarification could be very helpful in the debate between "intensivists" and onco-haematolo-

Correspondence to F. Blot.
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gists as to whether a cancer patient should be admitted to an ICU.

It is traditionally assumed that haematological malignancies are associated with a worse prognosis than solid tumours, in particular because of more severe and prolonged neutropenia [1]. Although some attempts have been made to define prognostic factors for cancer patients in an ICU [10], cases requiring mechanical ventilation (MV) [1], patients with haematological malignancies [2–6] or bone marrow transplant recipients [9], no study has so far focused on the early prognostic factors for neutropenic patients admitted to an ICU.

The purpose of this study was, therefore, to determine whether any of the characteristics present at the time of admission to an ICU could help to predict the outcome of this admission, and thereby guide decisions as to whether or not patients should be transferred to such units.

PATIENTS AND METHODS

The Institut Gustave Roussy is a 450-bed comprehensive cancer centre with a 15-bed medico-surgical intensive care unit.

For this study, we have reviewed the charts of all patients with chemotherapy-induced neutropenia referred to our ICU over a four-year period (1987–1991). During this period, 107 neutropenic patients were admitted (WBC count $<1000/mm^3$ and/or neutrophil count $<500/mm^3$).

The following characteristics were recorded at the time of admission: age, sex, the reason for admission, characteristics of neutropenia (severity and duration before admission), characteristics of the underlying malignancy and severity scores.

Malignancies were classified according to type (i.e. solid tumour or haematological malignancy), status (initial presentation or relapse, remission or progression, presence of bone marrow involvement) and the duration of cancer prior to admission to the ICU. The severity of the malignancy was assessed using MacCabe's score [16]: none of our patients was scored A (non-fatal disease). Chronic leukaemia and myeloproliferative syndrome, multiple myeloma, malignant lymphoma below stage IV, any malignancy necessitating bone marrow transplantation, and non-metastatic solid tumour were recorded as ultimately fatal within 5 years (score B). Acute leukaemia, primitive or blastic transformation of chronic leukaemia, stage IV lymphoma and metastatic solid tumours were recorded as rapidly fatal within 1 year (score C).

The severity of the acute illness admission to the ICU was based on the type and number of organ system failures (OSFs) according to Knaus's definitions [17]. OSFs were assessed within 24 h of admission to the ICU as cardiovascular, respiratory, renal, haematological, neurological and hepatic (Table 1). Hepatic failure was defined as a bilirubin level >60 mg/l and a prothrombin time >4 s above the reference value [18]. By selection, all the patients had haematological failure at admission. Two severity scores were recorded: the Simplified Acute Physiological Score (SAPS) [19], calculated from age, and the sum of 13 weighted points representing the extent of physiological disturbances, and SAPS II, calculated from 14 objectively weighted acute illness points and two chronic variables (age and chronic health points), taking into account the diagnosis of haematological malignancy or metastatic cancer, thus making this score more relevant to cancer patients [20].

The endpoint studied was outcome in the ICU.

Means were compared by Student's *t*-test, and percentages by the Chi-squared test or Fisher's exact test. Variables found to be associated with mortality with an α risk of 5%, or variables suspected to have any effect on the outcome, were included in a logistic regression model.

Table 1. Definitions of organ system failures (OSFs) according to the definitions of Knaus [17]

If the patient had one or more of the following during a 24-h period (regardless of other values), OSF existed on that day.

I. Cardiovascular failure (presence of one or more of the following):
   - A. Heart rate ≤49 mmHg
   - B. Mean arterial blood pressure ≤49 mmHg
   - C. Occurrence of ventricular tachycardia and/or ventricular fibrillation
   - D. Serum pH ≤7.24 with a $PaCO_2$ of ≤49 mmHg.

II. Respiratory failure (presence of one or more of the following):
   - A. Respiratory rate ≤5/min or ≥49/min
   - B. $PaCO_2$ ≥50 mmHg
   - C. $AaDO_2$ ≥350 mmHg
   - D. Dependent on ventilator on the fourth day of OSF.

III. Kidney failure (presence of one or more of the following, excluding patients on chronic dialysis before hospital admission):
   - A. Urine output ≤479 ml/24 h or ≤159 ml/8 h
   - B. Serum BUN ≥100 mg/100 ml
   - C. Serum creatinine ≥3.5 mg/100 ml.

IV. Haematological failure (presence of one or more of the following):
   - A. White blood cell count $\leq 1000/mm^3$
   - B. Platelets $\leq 20{,}000/mm^3$
   - C. Haematocrit ≤20%.

V. Neurological failure:
   - Glasgow Coma Score ≤6 (in absence of sedation at any one point in day).

VI. Liver failure (presence of both the following):
   - A. Bilirubin >60 mg/l
   - B. Prothrombin time >4 s above the reference value.

Pa, arterial partial pressure; AaD, alveolar–arterial oxygen gradient; BUN, blood urea nitrogen.

Table 2. Characteristics of patients at ICU admission

Parameters	
Male/Female (*n*)	72/35
Age (years)	36.8 ± 17.0
Chronic illness	*n* (%)
Tumour type	
solid tumour	50 (47)
haematological malignancy	57 (53)
Bone marrow involvement	42 (39)
Bone marrow transplantation	27 (25)
Tumoral progression	72 (67)
Duration of cancer (months)	19.8 ± 29.3
MacCabe score C	60 (56)
Severity scores	
SAPS	19.56 ± 5.15
SAPS II	57.85 ± 17.26
OSF	2.13 ± 0.99
Reason for admission*	
Respiratory	44 (41)
Cardiovascular	22 (21)
Renal/Metabolic	9 (8)
Neurological	15 (14)
other	17 (16)
Organ system failures†	
Haematological	107 (100)
Respiratory	57 (53)
Cardiovascular	31 (29)
Renal	20 (19)
Neurological	10 (9)
Hepatic	3 (3)

Data are means ± S.D.
*Main reason for admission of each patient (Total = 7).
†Some patients had several organ failures (Total = 228).
SAPS, simplified acute physiological score; OSF, organ system failure.

RESULTS

The characteristics of the 107 patients are shown in Table 2.

According to OSF criteria, 74 patients (69%) had failure of at least one organ system on admission, in addition to haematological failure. The two main reasons for admission to the ICU were the onset of a cardiovascular or a respiratory dysfunction. 31 patients had cardiovascular failure (29%). 57 patients (53%) had respiratory failure; note that the latter patients were more likely to experience cardiovascular failure than patients without respiratory failure (44 versus 12%, respectively, $p = 0.0003$).

57 of the 107 patients (53%) had haematological malignancy, and 50 (47%) a solid tumour. When the characteristics of these two groups of patients were compared (Table 3), patients with a haematological malignancy were, as expected, younger than those with a solid tumour, and more of them were in remission. It is noteworthy that more haematological malignancy patients presented with respiratory failure at admission, and thus more of them required mechanical ventilation in the ICU. In addition, their SAPS and SAPS II scores were higher than those of patients with a solid tumour. However, the number of OSFs was not significantly different between the two groups.

The overall mortality rate in the ICU was 55% (59/107). None of the prognostic factors was related to any characteristic of the underlying malignancy (Table 4) nor was there a significant difference in mortality rates for patients with haematological malignancy and patients with solid tumour (61 versus 48% $p = 0.16$, Figure 1). For the group of patients with haematological malignancy, the differences as regards the mortality rate were not significant between patients with lymphoma (21/31: 68%), leukaemia (13/24: 54%) or other blood diseases (1/2: 50%). In addition, the duration of neutropenia before admission to the ICU was comparable for survivors and non-survivors (12.9 ± 37.3 days and 11.0 ± 17.8 days, respectively, $p = 0.74$).

Respiratory and cardiovascular failures were significantly correlated with higher mortality (Table 4). All 3 patients with hepatic failure at the time of admission to the ICU subsequently died. The number of organ failures at the time of admission was larger in non-survivors (2.61 ± 0.93) than survivors (1.54 ± 0.71, $p < 0.0001$). The mortality rate in the ICU according to the number of OSFs at admission is shown in Figure 2.

The severity scores, calculated on admission to the ICU, were higher among the patients who died. Thus, the SAPS scores for survivors and non-survivors were, respectively, 17.6 ± 4.4 and 21.1 ± 5.2 ($p = 0.0004$), and the SAPS II scores, 48.4 ± 13.7 and 65.7 ± 16.0 ($p < 0.0001$).

Using multivariate analysis, only the number of OSFs and the presence of respiratory failure on admission were included in the logistic model as reciprocating additional predictive information (Table 5). According to the absence or presence of respiratory failure, the risk of death in the ICU increased from 40 to 67% in patients with two OSFs and from 50 to 90% in patients with three. None of the characteristics of the underlying malignancy or of the SAPS scores were of prognostic significance when respiratory failure was present.

In the present study, mortality was recorded at the time of discharge from the ICU. However, particular attention was paid to the cases of the 6 patients who died during the hospital stay after discharge from the ICU. All of them died between days 20 and 60 after this discharge, but their death was totally unrelated to the complication necessitating admission to the ICU or to any event that occurred during their stay in the ICU. The overall mortality rate in hospital was 61%. When the prognostic factors were studied, similar results were obtained for hospital and ICU mortality (unreported data).

DISCUSSION

The usefulness of intensive care for cancer patients remains highly controversial, mainly because of their elevated mortality [1–15]. However, mortality rates obviously differ according to the subsets of cancer patients considered. Among these subsets, neutropenic patients are thought to have the worst prognosis, with a mortality rate as high as 90% in some series [5, 11]. Oncologists and intensivists are in great need of objective early reproducible criteria to guide their decision as to whether such neutropenic patients should be transferred to an ICU when life-threatening complications occur, given their expected prognosis.

The objective of this study was to try to determine prognostic factors of the outcome of a stay in an ICU before the patient is referred to such a unit. For this reason, only the variables present at the time of admission to the ICU were taken into account in this analysis. This was not the case in the other published series, for which prognostic factors were

Table 3. Characteristics of patients with solid tumour or haematological malignancy

	Haematological malignancy ($n = 57$) n (%)†	Solid tumour ($n = 50$) n (%)†
Male/Female	38/19	34/16
Age	33.3 ± 16.1 years	40.8 ± 17.3 years
Duration of cancer	21.7 ± 25.5 months	17.6 ± 33.2 months
MacCabe score C*	38 (67)	22 (44)
Tumoral progression*	33 (58)	39 (78)
Bone marrow involvement*	37 (65)	5 (10)
Bone marrow transplantation	18 (32)	9 (18)
Allogenic transplantation	12	0
Duration of neutropenia*	25.4 ± 36.6 days	8.5 ± 8.9 days
Minimal WBC count	187 ± 186 per mm^3	236 ± 192 per mm^3
Organ failures at ICU admission		
Respiratory failure*	38 (67)	19 (38)
Haemodynamic failure	15 (26)	16 (32)
Renal failure	8 (14)	12 (24)
Mechanical ventilation*	42 (74)	27 (54)
Haemodialysis	7 (12)	9 (18)
Severity scores at ICU admission		
SAPS	20.5 ± 4.8 score	18.5 ± 5.4 score
SAPS II*	63.1 ± 16.4 score	51.7 ± 16.3 score
OSF	2.23 ± 0.91 score	2.02 ± 1.08 score
ICU stay	10.6 ± 12.2 days	8.1 ± 10.0 days
Mortality rate in the ICU	35 (61)	24 (48%)

*Haematological malignancy versus solid tumour: $p < 0.05$.
†n (%) unless otherwise specified.
Data are means ± S.D.
SAPS, simplified acute physiological score; OSF, organ system failure.

Table 4. Prognostic factors recorded at ICU admission

		Mortality	
	N	n	(%)
Underlying malignancy			
Type of malignancy			
haematological malignancy	57	35	(61)
solid tumour	50	24	(48)
Tumoral progression			
yes	72	38	(53)
no	35	21	(60)
Bone marrow involvement			
yes	42	22	(52)
no	65	37	(57)
Bone marrow transplantation			
yes	27	18	(67)
no	80	41	(51)
MacCabe score			
B	47	30	(64)
C	60	29	(48)
Organ system failures			
Cardiovascular failure			
yes	31	25	(81)
no	76	34	(45)
Respiratory failure			
yes	57	46	(81)
no	50	13	(26)
Renal failure			
yes	20	13	(65)
no	87	46	(53)
Neurological failure			
yes	10	8	(80)
no	97	51	(53)
Hepatic failure			
yes	3	3	(100)
no	104	56	(54)
Total	107	59	(55)

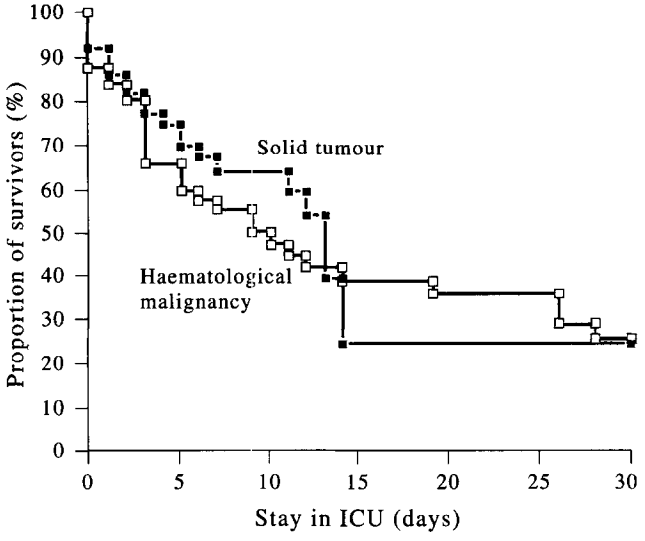

Figure 1. Probability of survival at 30 days, according to whether the underlying disease is haematological malignancy or solid tumour (Chi-squared test: $p = 0.16$).

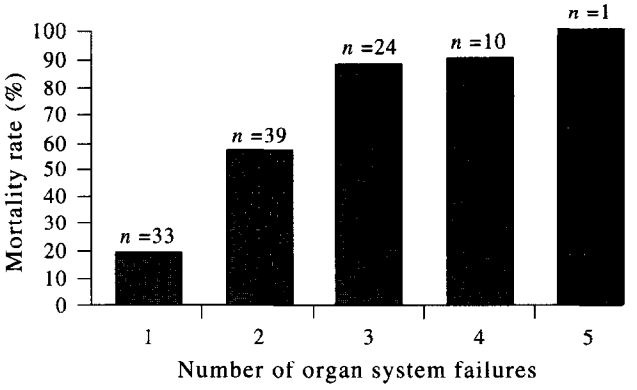

Figure 2. Mortality rate according to the number of organ system failures (OSFs) present at ICU admission.

analysed through variables emerging during the stay in the ICU, such as the summed number of organ systems involved, the duration of mechanical ventilation, the length of the ICU stay or subjective factors such as the need for life-saving techniques [1, 2, 4, 8, 11]. Furthermore, in most series, neutropenic patients were seldom studied as a specific subset admitted to an ICU, as the patients evaluated either did not require intensive support [6] or were not all neutropenic [4].

In the present study, we attached special importance to the prognosis for neutropenic patients in an ICU. In addition, all the parameters studied were based on objective and widely accepted criteria, such as the diagnosis and status of the underlying malignancy, the previous duration of cancer and neutropenia, or MacCabe's score, which is considered to reflect accurately the severity of the underlying disease [16]. Similarly, the definitions of acute failures [17, 18] and SAPS and SAPS II severity scores [19, 20], recorded within 24 h of admission to ICU, are widely used by intensivists to classify and evaluate the severity of disease correctly.

Unlike other authors, we recorded mortality at the time of discharge from the ICU. This end-point, i.e. mortality in the ICU, seems to us justification for admission to an ICU, since it indicates the specific impact of management in an ICU on overall outcome. The death of 6 patients during their hospital stay, after their discharge from the ICU, was totally unrelated to the complication necessitating their admission to the ICU and to any event that occurred during their stay in the ICU. When the end-point of mortality in the ICU, therefore reflecting the effect of the stay in the ICU accurately, and overall hospital mortality were studied, similar results were obtained (unpublished data).

Chemotherapy-induced neutropenia, secondary to haematological malignancies, was previously shown to be associated with a poorer prognosis than that noted for the treatment of solid tumours, because this neutropenia is usually more severe and lasts longer [1, 22]. However, a poor prognosis in the ICU was also reported in the presence of progressive or unresponsive malignant disease [2], an increasing number of metastic sites [7], or prolonged granulocytopenia [2, 23]. Others have stated that the type of malignancy is not predictive of death in an ICU [10, 24]. In fact, with the development of highly myelosuppressive chemotherapy regimens for both haematological and solid malignancies, severe and prolonged neutropenia may be observed in any type of cancer. In our study, although the duration of neutropenia was significantly greater for patients with haematological malignancy, the severity of neutropenia did not differ for different types of tumour. In addition, although the severity of the chronic illness (MacCabe score) and of the acute disorders (SAPS II) were greater in patients with haematological malignancy, due in part to a higher incidence of respiratory failure, there was no significant difference between both groups as regards the ICU mortality rate or the duration of the stay in the ICU. However, this absence of a significant difference must be interpreted with caution given the retrospective design of the study, because it may be due to the relatively small number of patients studied.

In contrast to its usefulness in certain populations with comparable mortality rates, such as patients with severe sepsis syndrome [25], the MacCabe classification [16] did not prove helpful for neutropenic patients in an ICU. Moreover, it was published a long time ago and may no longer accu-

Table 5. Prognostic factors at ICU admission: multivariate analysis by logistic regression

	Univariate analysis	Multivariate analysis	
	P	*P*	RR*
Number of OSFs	<0.001	<0.001	2.7
Respiratory failure	<0.001	<0.001	3.7
Cardiovascular failure	<0.001	0.10	
Characteristics of the underlying malignancy (haematological versus solid tumour, tumoral progression, duration and severity of neutropenia, MacCabe's score)	>0.1	>0.8	
SAPS II	<0.001	0.07	

*Relative risk.
SAPS, simplified acute physiological score; OSF, organ system failure.

rately reflect the real weight of each underlying disease. The new therapeutic approaches proposed for cancer patients during the past decade now pose the problem of elaborating an updated and accurate classification of diseases.

As shown by the present multivariate analysis, the prognosis for neutropenic patients in an ICU is clearly independent of the type and progression of cancer, and only depends on the presence, nature and number of acute organ failures. As regards outcome in the ICU, the number of OSFs, and among them the presence of respiratory failure, were the best predictors of death. With regard to this criterion, the number of OSFs at the time of admission to the ICU appears to be the best prognostic factor. As shown in Figure 2, the mortality rate rose from 18 to 56% and 88% when 1, 2 and 3 or more OSFs, respectively, were present at admission. Similar results were previously reported by others for the total number of OSFs (i.e. recorded throughout the stay in an ICU) [1–3].

Among all the organ failures, acute respiratory failure had the strongest effect on outcome. This is in accordance with other reports, if we consider mechanical ventilation an accurate reflection of severe respiratory failure [2–4, 6, 7, 10, 11]. In previous studies, the duration of mechanical ventilation was reported to be an important variable in assessment of the prognosis for cancer patients, especially the duration of mechanical ventilation during neutropenia [9, 11]; in Schuster's study, a duration of mechanical ventilation during neutropenia exceeding 5 days was consistently associated with a fatal outcome in the ICU [11]. Although this variable, by definition not available at admission to an ICU, was beyond the scope of the present study, it is surely of value for periodical reassessment of the justification of the ICU stay for mechanically ventilated neutropenic patients. Considering the possible harmful effects of mechanical ventilation, every effort should be made to reduce these effects or to curtail the ICU stay, by means such as early tracheotomy [26, 27] or non-invasive ventilation [28]. However, the efficacy of such approaches has not yet been demonstrated.

As previously reported [4, 6], cardiovascular failure was also associated with a poor prognosis in the present univariate analysis. However, since cardiovascular and respiratory failures were significantly associated, it is difficult to define exactly their respective roles in our study. Incidently, the prognostic value of cardiovascular failure disappeared in the multivariate analysis.

Finally, in this investigation, hepatic failure was consistently associated with a fatal outcome, but the small size of the subset of patients concerned makes it impossible to draw definite conclusions regarding the significance of hepatic failure. The absence of statistical significance for neurological and hepatic failures may be due to the insufficient number of patients studied in our analysis (i.e. to a type II statistical error).

Only organ system failures, which constitute objectively defined syndromes and not aetiological diagnosis, were considered in this study. Consequently, the diagnosis of infection or sepsis was not taken into account and was, therefore, not included in the prognostic factors recorded at ICU admission. In any case, a diagnosis of sepsis in a subset of immunocompromised patients is too often based on subjective or doubtful considerations, making this entity too uncertain and not reproducible from one physician to another. Similarly, the Systematic Inflammatory Response Syndrome [29] was too uncertain and difficult to record, given the retrospective design of the present study. We attempted, however, to assess the influence of a proven or suspected infection at admission to the ICU on the prognosis of neutropenic patients and found no significant difference in terms of ICU mortality (infection: 58.5% versus no infection: 45%).

It should be emphasised that the results of such studies only provide information concerning subgroups of patients, but remain controversial for individual management of a given patient. Nevertheless, the information acquired in such studies may be very useful, especially when the probability of curing the malignant disease is poor.

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