The ICU Trial: A new admission policy for cancer patients requiring mechanical ventilation*

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Objective: Cancer patients requiring mechanical ventilation are widely viewed as poor candidates for intensive care unit (ICU) admission. We designed a prospective study evaluating a new admission policy titled The ICU Trial.

Design: Prospective study.

Setting: Intensive care unit.

Patients: One hundred eighty-eight patients requiring mechanical ventilation and having at least one other organ failure.

Interventions: Over a 3-yr period, all patients with hematologic malignancies or solid tumors proposed for ICU admission underwent a triage procedure. Bedridden patients and patients in whom palliative care was the only cancer treatment option were not admitted to the ICU. Patients at earliest phase of the malignancy (diagnosis <30 days) were admitted without any restriction. All other patients were prospectively included in The ICU Trial, consisting of a full-code ICU admission followed by reappraisal of the level of care on day 5.

Measurements and Main Results: Among the 188 patients, 103 survived the first 4 ICU days and 85 died from the acute illness.

Hospital survival was 21.8% overall. Among the 103 survivors on day 5, none of the characteristics of the malignancy were significantly different between the 62 patients who died and the 41 who survived. Time course of organ dysfunction over the first 6 ICU days differed significantly between survivors and nonsurvivors. Organ failure scores were more accurate on day 6 than at admission or on day 3 for predicting survival. All patients who required initiation of mechanical ventilation, vasopressors, or dialysis after 3 days in the ICU died.

Conclusions: Survival was 40% in mechanically ventilated cancer patients who survived to day 5 and 21.8% overall. If these results are confirmed in future interventional studies, we recommend ICU admission with full-code management followed by reappraisal on day 6 in all nonbedridden cancer patients for whom lifespan-extending cancer treatment is available. (Crit Care Med 2007; 35:808–814)

KEY WORDS: mechanical ventilation; cancer; neutropenia; septic shock; dialysis; organ failure

ver the last 2 decades, the management of critically ill cancer patients has changed dramatically. Dismally low survival rates in cancer patients requiring life-sustaining treatment were reported in the 1980s, leading experts to discourage intensive care unit (ICU) admission of cancer patients (1–3). In addition, prolonged mechanical ventilation was considered inappropriate in recipients of bone marrow transplantation (4–8). Consequently, procedures for triaging cancer patients to the ICU have been developed (9, 10). However, the perfor-

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mance of the selection criteria used for triage has not been fully evaluated.

The limited performance of ICU admission criteria for predicting outcomes (11) prompted us to broaden our ICU admission policy for critically ill cancer patients (3). The ICU Trial strategy is designed to improve the chances of survival in critically ill cancer patients who could receive life-extending cancer treatment provided they survive an episode of very severe acute disease. According to our new policy, patients who are bedridden, or for whom no lifespan-extending cancer treatment is available, are not admitted to the ICU. Patients scheduled for cancer treatment or having a good chronic performance status are admitted for a trial of ICU management (Fig. 1) (12). This ICU trial consists of full-code treatment for 4 days followed, on day 5, by a reappraisal of the appropriate level of care. The rationale for this ICU trial strategy is based on five facts that have emerged from recent studies: a) survival has improved in critically ill cancer pa-

tients, including those who need ventilatory support (10, 13–15), vasopressors (16), or renal replacement therapy (17, 18); b) classic predictors of mortality may have lost much of their value (14, 19-21); c) because of patient selection, the characteristics of the malignancy are not associated with ICU survival (22, 23); d) physiologic scores do not perform well enough to assist in ICU triage (24) and the use of specific scores (25) remains controversial (26, 27); and e) mortality in critically ill patients depends on the nature and number of organ failures (16, 28–30). This is true not only at ICU admission but even more so 3 days (16, 28, 29) to 5 days (4, 22) after ICU admission.

We conducted a prospective study to evaluate survival in cancer patients admitted for an ICU trial, requiring mechanical ventilation during the ICU stay, and having at least one other organ dysfunction. In addition, we sought to identify criteria for deciding when to withhold or withdraw life-sustaining treatment on

^{*}See also p. 965.

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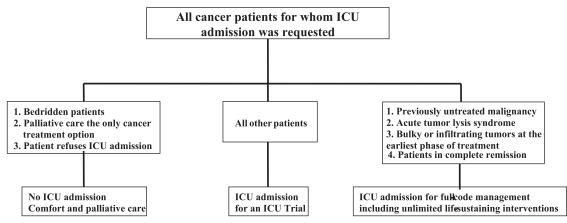


Figure 1. Intensive care unit (ICU) admission policy initiated in 2001 at the Saint-Louis Hospital.

day 5 of an ICU trial in a patient with persistent organ failures.

PATIENTS AND METHODS

The ethics committee of the French Society for Critical Care approved the study in December 2001. All patients and family members gave informed consent to participate in the study. Information on the study was provided before ICU admission, both by hematologists or oncologists and by intensivists. This information included the nature of the acute disease, the required treatments, and the uncertainty of the prognosis (described as follows: "death is the most likely outcome"). In addition, all patients and family members were told that the prognosis would be reassessed after a few days in the ICU and that ICU admission was being offered as a temporary measure although ICU refusal was recommended in current guidelines (3). We focused on patients who were still alive after 4 days in the ICU because of previous studies reporting disastrous survival rates in critically ill cancer patients needing mechanical ventilation for ≥ 5 days (4, 22). At the time of the study, advance directives were not available in France (31). Two patients and three family members refused the ICU Trial.

Description of the Saint-Louis Teaching Hospital. The Saint-Louis Teaching Hospital is a 650-bed university hospital with 330 hematology and oncology beds, where about 600 patients with newly diagnosed cancer are admitted each year. The hospital mortality rate in the eight oncology wards is about 5%. The medical ICU is a closed 12-bed unit that admits 600-650 patients per year, including about 130 cancer patients, most of whom have hematologic malignancies. The daytime staff consists of five intensivists and three residents and the nighttime staff of one senior intensivist and one resident. In addition, a senior hematologist is on duty 24 hrs a day for the hematology and solid-tumor wards.

ICU Admission Procedure Used Routinely at the Saint-Louis Teaching Hospital and Patient Selection Criteria for The ICU Trial Strategy. ICU admission is considered routinely when a cancer patient has at least one acute organ failure. First, the patient is evaluated jointly by a senior intensivist and the ward oncologist in charge of the patient. The final decision regarding ICU admission is then taken by the senior intensivist, who records the decision in the patient's chart as admission or refusal. In case of refusal, a second intensivist is involved in the decision (11). Figure 1 depicts our admission policy to the ICU. To admit a patient, intensivists require patient consent and availability of lifespanextending treatment options for the malignancy (i.e., patients not in palliative care). In addition, bedridden patients are not admitted to the ICU (11). Bedridden patients are those who have spent most of their time at bed over the last 3 months preceding ICU admission and who have lost their ability to fully care for themselves. The information was found in the patient's medical chart and confirmed by the oncologist or the hematologist who shared the decision of ICU admission (11). Patients with organ failures and/or sepsis as the inaugural symptoms of their malignancies, those with tumor lysis syndrome or malignant organ infiltration, and those with complete remission of their malignancies are admitted with a full-code status (32). Criteria for the ICU Trial strategy are a) remission or stable disease with scheduled therapeutic intensification; b) good health status with a prognosis that is unclear or not yet assessable; or c) availability of potentially lifespan-extending cancer treatment. Full-code ICU treatment is given; starting on day 5, the level of care is assessed daily based on the clinical course.

Inclusion criteria for the present study were eligibility for an ICU trial, need for mechanical ventilation during the ICU stay, and presence of at least one organ failure other than hematologic failure. To ensure homogeneity of our study population, we did not include HIV-positive cancer patients or recipients of allogeneic stem cell transplants, two populations in which survival is extremely low after mechanical ventilation (6, 8). Between December 2001 and December 2004, we included consecutive patients meeting our inclusion and noninclusion criteria.

Data Collection. For each study patient, data reported in Tables 1 and 2 were collected. Leukopenia was defined as a leukocyte count <1000/mm³. The Logistic Organ Dysfunction (LOD) score was collected daily during the first 3 days and then every 3 days until ICU discharge (33). This score assesses the nature and the severity of organ failures in ICU patients and has been extensively validated in overall ICU populations (33) and in critically ill cancer patients, at admission and on day 3 (16, 29). ALOD score on day 3 was defined as (day 3 - day 1 LOD score/day 3 LOD score) (16) and Δ LOD score on day 6 as (day 6 - day 1 LOD score/day 6 LOD score). The date of ICU discharge, length of ICU stay, and status at ICU and hospital discharge were also collected. The definitive diagnoses as determined by consensus among three intensivists (EA, GT, and MD) were recorded.

Treatment-limitation decisions were made according to current guidelines (34). Thus, treatment limitations occurred after at least two staff meetings during which all nurses, intensivists, and the hematologist/oncologist stated their conviction that death would occur in the short term despite support for a new organ failure or maintenance of full life support. Treatment limitations were never discussed before day 5. Treatment-limitation decisions were recorded in detail in the patient's medical chart (35). Family members were informed at least once a day by the ICU physician and hematologist/oncologist throughout the ICU stay. When family members were willing to participate in treatment decisions, they were encouraged to do so.

Statistical Analysis. Survival after hospital discharge was recorded for all patients. Results are reported as medians and quartiles (interquartile range) or numbers (%). For the evaluation of patient characteristics, categori-

Table 1. Characteristics of the malignancy

Patients	Early Decedents $(n = 85)$	Decedents After Day 4 $(n = 62)$	Hospital Survivors $(n = 41)$	p Value
Age, yrs (IQR)	51 (36-67)	56.8 (47.2–66.7)	44.7 (42.1–58.8)	.05
Male gender, n (%)	55 (64)	43 (69.3)	26 (63.4)	.6
Comorbidities, n (%)				
Hypertension	30 (35.3)	19 (30.6)	5 (12.1)	.03
COPD	8 (9.4)	7 (11.3)	6 (14.6)	.7
Chronic heart failure	4 (4.7)	3 (4.8)	2 (4.8)	.9
Long term steroids	1 (1.2)	3 (4.8)	3 (7.3)	.6
One comorbidity	29 (34.1)	35 (56.4)	19 (46.3)	.4
Chronic health status, n (%)	× ,			
Normal or slight alteration	74 (87.1)	49 (78.9)	32 (78)	.7
Altered	11 (12.9)	13 (20.9)	9 (21.9)	.9
Bedridden	0	0	0	_
Characteristics of the malignancy, n (%)				
Acute leukemia	25 (29.4)	20 (32.3)	11 (26.8)	.5
Chronic lymphocytic leukemia	5 (6)	3 (4.8)	2(4.9)	.9
Non-Hodgkin's lymphoma	20 (23.5)	14 (22.6)	11 (26.8)	.6
Multiple myeloma	10 (11.8)	7 (11.3)	4 (9.7)	.8
Lung and breast cancer	12 (14.1)	8 (12.9)	6 (15.3)	.8
Other solid tumor	13 (15.3)	10 (16.1)	7 (17)	.9
Time from diagnosis, days (IQR)	54 (11-179)	37 (6-340)	67 (15-343)	.8
Treatments received for the malignancy				
Courses of chemotherapy, n (IQR)	3 (1-3)	2.5(0-4)	3.3 (0-5.25)	.7
Autologous stem cell transplantation, n (%)	10 (11.7)	9 (14.5)	5 (12.9)	.8
Status of the malignancy at ICU admission, n (%)				
First 3 months of the treatment	45 (52.9)	36 (58)	23 (56)	.4
Remission or stability	40 (47.1)	21 (34)	16 (39)	.6
Relapse	0	4 (6.5)	2 (5)	.2

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Statistical comparisons are made between decedents after day 4 and hospital survivors.

Table 2. Organ failure a	and therapeutic	interventions i	in the	intensive	care unit	(ICU)
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Patients	Early Decedents $(n = 85)$	Decedents After Day 4 $(n = 62)$	Hospital Survivors $(n = 41)$	p Value
Treatments received before ICU admission, n (%)				
Antibiotics	79 (92.9)	55 (88.7)	39 (95)	.2
Fluid expansion	77 (90.6)	22 (35.5)	18 (43.9)	.06
Oxygen	48 (56.5)	40 (64.5)	22 (53.6)	.3
G-CSF	4 (4.7)	4 (6.4)	7 (17)	.3 .2 .4
Time from hospital to ICU admission, days (IQR)	4(0-7)	11.3 (1-15)	13.8 (0-23)	.4
Time from symptom onset, days (IQR)	1 (0-3)	5.9 (1-7)	6.3(1-10)	.9
Leukopenia at ICU admission, n (%)	19 (22.3)	14 (22.5)	13 (31.7)	.3
Reasons for ICU admission (one or more), n (%)	- (· · · · ·)	()	- (- · ·)	
Septic shock	39 (45.9)	24 (38.7)	17 (41.5)	.07
Acute respiratory failure	80 (94.1)	44 (70.9)	22 (53.6)	.07
Acute renal failure	5 (5.9)	8 (12.9)	4 (9.7)	.7
Coma	11 (12.9)	6 (9.7)	1(2.5)	.2
Reasons for mechanical ventilation (one or more)	(,		(
Acute respiratory failure, n (%)	60 (70.6)	41 (66.1)	29 (70.7)	.6
Shock, n (%)	44 (51.8)	25 (40.3)	16 (39)	.3
Coma, n (%)	11 (12.9)	17(27.4)	13 (31.7)	.6
Length of mechanical ventilation, days (IQR)	3 (1-4)	11.3 (5-15)	12.4(4.5-16)	.1
Pao ₂ /Fio ₂ ratio (IQR)	84 (78-113)	147 (76–160)	170 (129-205)	.02
Other life-sustaining interventions	- ()		(,	
Noninvasive mechanical ventilation, n (%)	7 (8.2)	30 (43.38)	13 (31.7)	.07
Vasopressors, n (%)	80 (94.1)	53 (85.5)	25 (61)	.01
Duration of vasopressor use, days (IQR)	3 (1-4)	8 (3–13)	4(2-11)	.01
Maximum dosage of epinephrine or norepinephrine, mg/hr (IQR)	5 (1-11)	9.8 (3-11)	6.3(2-10)	.09
Renal replacement therapy, n (%)	17 (20)	20 (32.3)	7 (17.1)	.06
LOD score at day 1 (IQR)	12 (8.5-13.5)	6 (3–9)	5 (3-8)	.1
LOD score at day 2 (IQR)	15 (14–17)	5 (3-8)	5 (4-8)	.9
LOD score at day 3 (IQR)	15 (13-17)	7 (4–9)	5 (3-7)	.01
Length of ICU stay, days (IQR)	3 (1-4)	13.7 (5–16)	19.8 (5-26)	.05

G-CSF, granulocyte colony-stimulating factor; IQR, interquartile range; LOD, Logistic Organ Dysfunction.

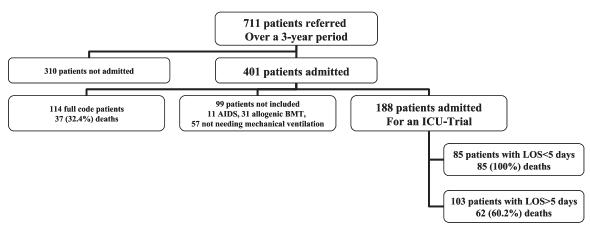


Figure 2. Patient flow chart. BMT, bone marrow transplant; ICU, intensive care unit; LOS, length of stay.

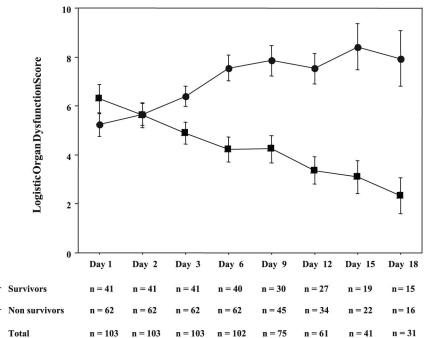


Figure 3. Changes in the Logistic Organ Dysfunction Score throughout the intensive care unit stay in survivors (*open triangles*) and nonsurvivors (*filled circles*).

cal variables were compared using the chisquare test or Fisher's exact test, as appropriate, and continuous variables using the nonparametric Wilcoxon test. Vital status at hospital discharge was known for all study patients. A multivariate logistic regression model was performed. Every variable yielding p < .20 by univariate analysis was introduced. All tests were two-sided, and p values <.05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC).

RESULTS

During the 3-yr study period, 711 patients were considered for ICU admission, including 310 who were not admitted and 401 who were admitted (Fig. 2). Among admitted patients, 114 were at the earliest phase of the malignancy and were admitted with nontrial full-code status, 42 were either HIV infected or recipients of allogeneic stem cell transplants, and 57 did not receive mechanical ventilation. The remaining 188 patients were given an ICU trial; they form the basis for this study. Among them, 85 died within the first 4 ICU days without treatment limitations and 103 survived the first 4 ICU days.

Tables 1 and 2 report patient characteristics as well as comparisons between decedents after day 4 and hospital survivors. The following results focus on the 103 patients alive on day 5. Among these

103 patients, there were 69 (67%) men and the median age was 55 (45-65) years. Chronic health status was considered normal or only slightly impaired in 81 (78.6%) patients. As shown in Table 1, most patients had acute leukemia or non-Hodgkin's lymphoma and 31 (30%) had a solid tumor. Fifty-nine (57.3%) patients had been diagnosed with malignancy within the last 3 months and were not assessable for response, 28 (27.2%) were in remission, nine (8.7%) had stable disease, and six (5.8%) had relapsing disease for which potentially lifespan-extending cancer treatment was available. Autologous stem cell transplantation had been performed in 14 patients and was scheduled to be done within the next 6 months in 31 (30%) patients. Leukopenia was found in 27 (26.2%) patients. Reasons for ICU admission were acute respiratory failure (n = 66, 64%), septic shock (n = 41, 39.8%), acute renal failure (n = 12, 11.6%), and coma (n = 7, 6.8%). At day 1, 42% of the patients had respiratory failure. 74% renal failure, 58% cardiovascular failure, 46% hematologic failure, 38% neurologic failure, and 20% hepatic failure.

As shown in Table 2, the leading reason for mechanical ventilation was acute respiratory failure. Intubation was performed after failure of noninvasive mechanical ventilation in 43 (41.7%) patients; 40 (38.8%) patients received fluid expansion, 78 (75.7%) received vasopressive agents, and 27 (26.2%) received renal replacement therapy.

Among the 103 day-5 survivors, respiratory and renal failures were the most common organ failures, followed by cardiovascular, hematologic, neurologic, and hepatic failures. A linear relation was found between the number of organ failures on day 6 and mortality. Mortality

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was 26% in patients with one organ failure on day 6, 55% in patients with two organ failures, 85% in patients with five organ failures, and 95% in patients with six organ failures. Figure 3 depicts LOD score changes during the ICU stay in patients who survived 5 days. From day 3 onward, the LOD score was significantly worse in nonsurvivors than in survivors. Time to initiation of life-sustaining treatments was also linked to mortality (Fig. 4). Among patients who survived 5 days, all patients who required initiation of endotracheal mechanical ventilation, vasopressors, or dialysis after 3 days in the ICU died. The discrimination of the LOD score for predicting hospital mortality in patients who survived 5 days was evaluated using receiver operating curves. The score on day 6 (area under the curve [AUC] 0.73 [0.69–0.80]) was more accurate than the score at admission (AUC $0.41 \ [0.36 - 0.47])$ or on day 3 (AUC 0.63 [0.57-0.69], p = .001 between LOD6 and LOD1, and p = .02 between LOD6 and LOD3). Similarly, the Δ LOD score on day 6 (AUC 0.72 [0.67–0.78]) was better than the Δ LOD score on day 3 (AUC 0.66 [0.61-0.72], p = .049).

Of these 103 day-5 survivors, 54 died in the ICU, including 48 after treatmentlimitation decisions, which were taken after 7 (5-17) days in the ICU. Decisions to forgo life-sustaining therapies included vasopressors for 21 patients, dialysis for 17 patients, fluid expansion for 11 patients, and reintubation after failure of extubation for four patients. Cardiopulmonary resuscitation was not performed in nine patients with cardiac arrest. Transfusions were withdrawn in 24 patients. Among the eight patients who died after ICU discharge, two were readmitted to the ICU and six died after treatmentlimitation decisions on the wards. Hospital mortality was 60.2% (62 patients). Hospital mortality of the entire cohort was 78.2% (147 deaths). The multivariate analysis did not identify significant independent predictors of hospital mortality.

DISCUSSION

ICU admission of cancer patients was controversial until recently (1-3, 36). Over the last decade, however, several studies reported increased survival rates in selected cancer patients admitted to the ICU (9, 14, 20, 22, 37), including those requiring mechanical ventilation (10, 15) or vasopressors (16) and those with neutropenia or autologous stem cell

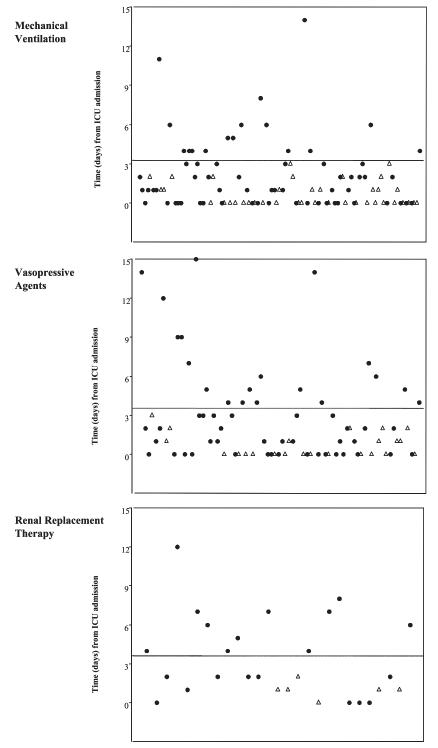


Figure 4. Time from intensive care unit admission to initiation of mechanical ventilation, vasopressors, and renal replacement therapy in patients who survived 5 days. Each subject is depicted separately. *Open triangles,* survivors; *closed circles,* nonsurvivors.

transplantation (19–21). In this study, we report outcomes in critically ill cancer patients who were given a trial of ICU management although they met current criteria for refusing ICU admission. Among 188 mechanically ventilated patients with at least two organ failures who received a trial of full-code ICU management, 103 were alive on day 5 including 41 patients who were discharged alive from the hospital. We focused on these 103 patients. Hospital survival was 40% in day 5 survivors and 21% overall, lending strong support to the ICU Trial strat-

egy for patients with a good performance status and lifespan-extending cancer treatment options. Furthermore, our results suggest that although treatment-limitation decisions should not be taken before day 6, initiation of mechanical ventilation, dialysis, or vasopressors after day 3 may indicate that death is inevitable.

This study is the first to investigate alternatives to ICU refusal in cancer patients requiring mechanical ventilation. The ICU Trial strategy has been used in neonates with severe brain damage (38). This strategy allows clinicians to better appraise the prognosis and relieves families from guilt due to a perception that nonadmission leads to loss of a chance of survival. A striking finding from this study is that patients with no hope for survival are easier to identify after an ICU trial.

Five points support full-code ICU management for a limited period in selected critically ill cancer patients who do not meet current criteria for ICU admission. First, the 21% survival rate in patients requiring prolonged mechanical ventilation and having at least two organ failures highlights the improvements achieved recently in critically ill cancer patients. Second, as previously reported (22-24, 30), the characteristics of the malignancy were not associated with shortterm survival. This fact is probably ascribable to patient selection by hematologists and oncologists. Third, data available at ICU admission were not significantly different between day-5 survivors and nonsurvivors. Fourth, organ failure scores at admission performed poorly, indicating that they cannot be used for triage. Last, as reported in cancer patients admitted for acute respiratory failure (29), time to initiation of lifesustaining therapies was associated with the outcome. More specifically, all patients who required the initiation of life-sustaining interventions after day 3 died. This finding may translate into a simple tool for decision making and family information.

We previously reported the performance of Δ LOD in critically ill cancer patients with septic shock (16). However, the course of organ failures over the first 5 ICU days, as reflected by Δ LOD on day 6, indicates that treatment-limitation decisions should not be taken before day 6.

Our study has several limitations. First, it was performed in a single institution. However, the presence of nine hematology and oncology wards in our hospital is a strong point. Furthermore, the

characteristics of our patient population, reasons for ICU admission, and survival rates are consistent with recent studies from several countries (14, 20, 21, 39), a fact that lends general relevance to our findings. Second, our triage criteria reported in Figure 1 clearly influenced our results. We recently reported that these criteria should be broadened, since they may lack specificity, in particular in the most severe patients (11). Nevertheless, we believe that ICU admission guidelines for cancer patients were based on studies that are no longer relevant (3) and that a broader admission policy is needed (40). Third, we focused on patients alive on day 5, in agreement with previous studies (4, 22). Cancer patients requiring invasive mechanical ventilation cannot recover fully from their acute illness within 4 days, given the time needed for organ failure resolution, weaning and extubation, and monitoring. Thus, in our study no patients were discharged alive before day 5. Treatment-limitation decisions are not taken before day 5 in our ICU. Therefore, we focused on patients still alive on day 5, for whom clinicians and surrogates need to determine how long life-sustaining therapies should be continued before the inevitability of death becomes evident. Nevertheless, we also provide complete data on the 85 patients who died before day 5. Fourth, 40% of patients alive on day 5 survived to hospital discharge. The overall survival rate in the 188 patients given an ICU trial was 21.8% (41 of 188). Nevertheless, it should be borne in mind that nearly all patients who died early had multiple organ failures and that we studied the sickest critically ill cancer patients. Thus, all study patients received mechanical ventilation and had at least two organ failures, and more than half the patients had at least three organ failures. In this population, we believe that a 20% survival rate indicates a duty to offer treatment. Fifth, using broader criteria for ICU admission might be associated with an increased proportion of deaths occurring after treatment-limitation decisions (41). This may translate into increased burden on the nurses and physicians and a higher rate of conflicts (42). This point needs to be evaluated. Similarly, since a high rate of distressing symptoms has been recorded in critically ill cancer patients, the preferences and values of patients and surrogates should be collected upstream from the ICU (43, 44).

CONCLUSIONS

This study provides new insights into the management of cancer patients requiring life-sustaining therapies. Providing an alternative to ICU refusal in patients with cancer for which potentially lifespan-extending cancer treatments were available resulted in a substantial survival rate. The results of this noninterventional study show that treatmentlimitation decisions should be considered only after at least 6 days of full-code ICU management. However, all the patients who required intubation, vasopressors, or dialysis after day 3 died. Interventional studies are needed to confirm these results and to highlight that in patients with malignancies requiring intensive care support, we should do everything that can be done.

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