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Causes of Death and Incidence of Life-support Techniques Limitations in Oncological Patients Dying in the ICU: A Retrospective Study

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Abstract

Background: Our objectives were to determine, for cancer patients dying in the ICU, the reasons for admission, the causes of death and the impact of life-support techniques limitations (LSTL).

Methods: This is a retrospective study including only cancer patients dying in the ICU.

Results: From 1st January 2008 to 31st December 2009, 658 patients were admitted in the ICU, 71 of whom had neoplastic disease and ultimately died after admission for a medical/surgical complications. Their principal characteristics were: men/women 38/33, median age 57 years, solid/haematological tumours 46/25. Solid tumours were mainly presenting at a metastatic stage (93.5%). Out of the 25 haematological patients, 6 were allograft recipients.

The most frequent causes of admission were respiratory failure (36.6%) and infection (47.9%). Infection was the cause of death in 53.5%. Twenty-one patients had LSTL at or during the first 24 hours of ICU admission, especially because of cancer progression. Another 33 had LSTL later due to clinical deterioration. Seventeen patients did not receive any LSTL; all died with mechanical invasive ventilatory support. Early LSTL is mainly related to cancer progression while late LSTL are often decided in front of unfavourable evolution of the acute complications in patients with better cancer prognosis.

Conclusions: This study, restricted to cancer patients dying in the ICU, showed that respiratory failure and infection were the leading cause of ICU admission. Infection was the first cause of death. The majority of the cancer patients dying in the ICU had LSTL. All patients with no LSTL died with mechanical invasive ventilatory support. Functional stages, the existence of an oncological treatment project and the evolution of complication leading to ICU admission have a major impact in the decision of LSTL.

Keywords: Cancer; Life-support techniques limitations; Mortality; Infection

Background

Advances have been made in the early diagnosis and aggressive management of patients with cancer, resulting in improvements in overall survival rates [1]. As a result, increasing number of patients are admitted to the intensive care unit (ICU), either for cancer-related complications or for treatment-associated side effects. Studies have reported very high mortality rates for cancer patients after a prolonged ICU stay, and aggressive management of life-threatening complications in these patients has been questioned [2,3]. However, recent studies have highlighted reduced mortality rates in critically ill cancer patients [4-7]. The development of new procedures, such as non-invasive mechanical ventilation [8] may also be useful in such patients. Nowadays, 15 % of patients admitted to European ICUs have cancer [9].

Death during the ICU stay occurs in 10-20% of the admitted patients [9,10], with as main predictors, multiple organ failure and severe underlying disease. Do not resuscitate (DNR) orders are now an accepted practice in ICUs. The frequency of DNR order is about 10% of ICU admissions [11,12]. The proportion of deaths in ICU patients occurring after decision to forego life-sustaining treatment has increased markedly in recent years [13]. In USA, up to 90% of patients who die in ICUs now do so following a decision to limit therapy [13]. Withholding and withdrawal of life-support therapies are widely practised in France where more than 50% of deaths are preceded by a decision to limit life-supporting therapies [10]. Patients with ICU DNR orders are older, more functionally impaired, have more comorbid illness, a higher severity of illness, and require the use of more ICU resources compared with patients without DNR orders [11]. However, decisions to forgo life-sustaining therapy in ICU patients remain independently associated with death after adjusting on comorbidities and severity at ICU admission [14].

In patients with cancer, the causes of death and the impact of limitation in the life-support techniques (LSTL) in the ICU are not well described in the literature. Our objectives were thus to determine the causes of death in relationship with the reasons for admission of cancer patients dying in the ICU and to assess incidence and impact of LSTL

Methods

This is a retrospective study, performed in the ICU of an academic oncological hospital (Institut Jules Bordet), including cancer patients dying after ICU admission for a medical or a surgical complication during a two years period (from 1st January 2008 to 31st December 2009). We excluded patients admitted in the ICU because of elective surgery or medical treatment.

The following data were retrospectively retrieved from the medical charts:

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- demographic data at ICU admission: age, gender
- disease characteristics: type of cancer, prior treatments, cancer phase [15] (diagnostic, curative, controllable but no more curable, pivotal when specific treatment aimed at cure or control has failed, palliative care; patients at palliative stage should not be admitted for critical care according to our ICU policy) oncological therapeutic project
- main reason for ICU admission
- existence of life-support techniques limitations (cardiopulmonary resuscitation, invasive mechanical ventilation and dialysis)
- main reason for life-support techniques limitations
- severity of illness assessed by the SAPS II score
- This study was accepted by our hospital ethical committee.

Statistical methods

Descriptive statistics were computed for all study variables. For demographics and clinical characteristics of the study groups, differences between groups were assessed using chi-square and Fisher's exact tests.

Results

From 1st January 2008 to 31st December 2009, 658 patients (780 admissions) were admitted in the ICU of whom 83.7% had a cancer. Out of them, 71 patients died after ICU admission (60 in the ICU and 11 in standard room where they were transferred for end of life care). Their main characteristics were: men/women 38/33, median age 57 years (19-85), solid/haematological tumours 46/25 (Table 1). Solid tumours were mainly presenting with a metastatic stage (93.5%). Out of the 25 haematological patients, 6 were allograft recipients. At ICU admission, 6 (8.4%) patients had a cancer in remission, 56 (78.9%) had an oncological therapeutic project (chemotherapy in 50 cases), 8 (11.3%) had a disease in a pivotal phase and for one (1.4%), oncological treatment was stopped according to patient wish. Median SAPS II score was 47 (range: 24-98). The most frequent cause of ICU admission (Table 2) was respiratory failure (36.6%) followed by hemodynamic problems (18.3%). Infection (47.9%) was the primary aetiology of organ failure.

Deaths were mainly due to hemodynamic (35.2%) and respiratory failures (32.4%) and infection (consisting mainly in septic shock and infectious pneumonia) was at the origin of death in 53.5% of the cases. In 55% of the cases, patients died due to the event leading to ICU admission while in 45%, death was the consequence of a further problem.

At ICU admission, 59 patients (83.1%) had no LSTL and 12 (16.9%) had LSTL, all because of cancer progression. Out of the 59 patients without LSTL at ICU admission, 42 had LSTL during ICU stay: 9 during the first 24 hours of ICU admission (6 because of cancer progression) and 33 patients later (26 due to the pejorative development of the acute complication).

Seventeen patients (all in remission or with an oncological therapeutic project) did not receive any LSTL of whom 76% had a haematological malignancy and 24% a solid tumour ($p<0.001$). All died with mechanical invasive ventilatory support. In 47% of these 17 patients, resuscitation manoeuvres were not applied at time of death. Twenty-three patients received LSTL before the need of intubation and invasive mechanical ventilation (IMV). For the 19 patients who received LSTL while on IMV, LSTL was most of the time (79%) justified by the pejorative evolution of the acute complication.

Discussion

Our study, restricted to cancer patients dying at the ICU, showed that respiratory failure and infections were the leading causes of ICU admission. Infection was the first direct cause of death in the ICU. We observed that the majority of the cancer patients dying in the ICU had LSTL during their stay. All patients with no LSTL died with invasive mechanical ventilatory support. Functional stages, the existence of an oncological treatment project and the type of complication leading

Sex (male/female)	38/33
Median age (min-max)	57 years (19-85)
Median SAPS II (min-max)	47 (24-98)
Type of cancer	46 solid tumour (64.8%) – 19 lung cancers (18 NSCLC + 1 SCLC) – 6 breast cancers – 6 digestive tumours – 5 gynaecologic cancers – 4 urologic cancer – 4 head and neck cancers – 1 melanoma – 1 sarcoma 25 haematological tumours (35.2%) – 14 acute leukemia – 7 lymphoma – 3 chronic leukemia – 1 myelodysplastic syndrome
Cancer phase	Diagnostic: 3 (4.2%) Curative: 8 (11.3%) Control: 52 (73.2%) Pivotal: 8 (11.3%)

NSCLC= non small cell lung cancer; SCLC=small cell lung cancer

Table 1: Patients characteristics.

Total number of admission	**71**	
Respiratory	**26 (36.6%)**	**21 infectious pneumonia** 1 alveolar haemorrhage 1 haemothorax 1 pneumothorax 1 bronchospasme 1 tumoral obstruction
Haemodynamic	13 (18.3%)	**7 septic shock** 3 hypovolemic shock **2 severe sepsis** 1 obstructive shock
Renal	8 (11.3%)	8 acute renal failure
Heart	6 (8.4%)	3 arrhythmia 2 pericardial effusion 1 syncope
Neurological	6 (8.4%)	**2 meningitis** 1 coma 1 status epilepticus 1 stroke 1 cerebral haemorrhage
Digestive	6 (8.4%)	3 hepatic failure **2 peritonitis** 1 bowel perforation
Metabolic	5 (7%)	3 tumoural lysis syndrome 1 hyperkaliemia 1 hypokaliemia
Haematological	1 (1.4%)	1 complicated disseminated intravascular coagulation

Infectious causes are in bold

Table 2: Patients admission causes.

to ICU admission have a major impact in the decision of LSTL. Early LSTL is mainly related to cancer progression while late LSTL are often decided in front of unfavourable evolution of the acute complications in patients with better cancer prognosis.

Our definition of a patient with LSTL is larger than the DNR/DNI definition as we also include patient for which we decide not to perform dialysis if necessary. This is also different of withdrawal of care where a life support technique has already been performed and where it is decided to withdrawn this technique. The high proportion of patients with advanced stage cancer reflects the population of our institute and can be explained by the fact that we are a reference centre for chemotherapy and phase I treatments and because we are not reluctant to take care of the patients if they have a therapeutic project. In our study, 11% of the patients had curative treatment 73% of the patients received a non-curative treatment and less than 10% had no active treatment of tumor but comfort measures only.

Infection was the cause of death in 53.5% in accordance with the published literature, showing the importance of infectious diseases in critically ill cancer patients [9]. In an autopsy series of cancer patients dying in the ICU, the direct cause of death was a major infection in 23.5% of the cases [16]. In the same way, in the European SOAP survey, where 15% of the patients had a malignancy (404 had solid tumours and 69 had haematological cancer), patients with cancer had a higher frequency of sepsis [9]. They were more often admitted to the ICU for sepsis and respiratory complications than other ICU patients [9]. These data could be explained by the immunosuppression due to cancer and/or its treatment.

At ICU admission, 17% of our patients who ultimately die in the ICU had LSTL, comparable to a general population where the frequency of DNR order is about 10% [11,12]. Our percentage of DNR order increased until 76% during the ICU stay. This percentage is higher than in a general French population where more than 50% of deaths are preceded by a decision to limit life-supporting therapies [10] but lower than in the USA where up to 90% of all patients who died in ICUs received a decision to limit therapy [13]. Tanvetyanon et al already observed that between patients who died of chronic heart failure (CHF) and those who died of metastatic cancer, there was no significant difference in prevalence of do-not-resuscitate orders. The majority in both groups received do-not-resuscitate orders before death (84% and 72%, respectively) but CHF patients received do-not-resuscitate orders later than did cancer patients (6.7 vs. 2.8 days, $p = 0.006$) [17]. In our series, the overall high rate of LSTL (76%) is probably in part due to hospital characteristics which are a cancer centre with a triage policy for ICU admission. This should have played a role and the results might thus not reflect attitudes in more general ICU.

When LSTL was decided before ICU admission or during the first 24 hours, the reason was most of the time the lack of control of cancer disease. When LSTL was decided later in the course of the ICU stay, this is mainly the cause of evolution of the initial acute complication. Indeed, we know that in-ICU prognosis is mainly determined by the acute physiological perturbations induced by the complication (and not by the characteristics of the neoplastic disease) but after recovery from the acute complication, further prognosis is determined by the characteristics of the underlying cancer disease [18]. So in patients with a relatively poor oncological prognosis, a decision to restrict critical care support is often taken. Seventeen patients (all in remission or with an oncological therapeutic project) did not receive any LSTL. This is easily explained: it is important to manage cancer patients with life-supporting techniques according to adequate cancer phase [15] and oncological project [19].

LSTL should be taken when a careful analysis of the patient's situation indicates that either the acute condition or the underlying disease will cause death rapidly, despite optimal treatment. However, the physician's values are also involved. Not every physician would make the same decision in a given situation [20]. The performance status of the patients just before the acute complication and the possibility of an active anti-cancer treatment after recovery of complication should be taken into account. In addition, the role of the patient and family in such decision of LSTL is crucial. Patients, families and clinicians may approach end-of-life discussions with different expectations and preference, influenced by religion, race, culture and geography [21]. A shared model of decision-making with values supplied by patients and families rather than physicians [22] should be used.

All the patients without LSTL died after intubation and with IMV support. Out of them, the majority died due to an anticancer treatment complication. However, in 8 of the 17 patients without limitation, cardiopulmonary resuscitation (CPR) manoeuvres were not applied. Hakim et al have already described that, in 5 teaching hospitals, 2% of seriously ill hospitalized patients died with no resuscitation attempted and with no order or decision documented in the chart [23]. A decision of no CPR can be taken without a formal written order in the patient's record when the situation is irreversible and the CPR maneuvers seem futile. In previous studies [24,25], it has been observed that CPR can be a successful technique in cancer patients especially for those in which cardiac arrest was the consequence of an acute insult but not in those in while it was the ultimate complication of multi-organ failure.

The question of who will live and who will die is fundamental. Some models have tried to respond to this important question. Models to assess probability of hospital mortality in cancer patients admitted to the ICU on the basis of variables readily obtained on admission were first published [26,27]. Then the same principles were applied to development and validation of a 72-h model [28] reflecting a period of time for clinicians to attempt to reverse a life-threatening complication. These scores could help in discussions with patients and their families to try and quantitate what their "chances" might be [29]. Indeed, it can be proposed a full critical care for 72 hours and then see if there is amelioration or not. In the last case, LSTL should be discussed with the patient and/or their family. The actual time spent in the ICU (admission to death) by the patients has not been evalutaed in this study, this could be assesse and analysed in a further study.

Conclusions

In conclusion, our retrospective study restricted to cancer patients dying at the ICU showed that respiratory failure and infections were the leading cause of ICU admission in this population and that infection was the first cause of death.

There is today few data about LSTL in cancer patients dying in the ICU. Functional stages, the existence of an oncological treatment project and the type of complication leading to ICU admission have a major impact in the decision of LSTL. Early LSTL is mainly related to cancer progression while late LSTL are often decided in front of unfavourable evolution of the acute complications in patients with better cancer prognosis. Patients without LSTL all received invasive reanimation procedures while dying at the difference of those with LSTL. In the future, it appears important to determine the reasons leading to a LSTL decision whatever in or outside ICU, taking into consideration e.g. the type and stage of cancer, the anticancer treatment or the type of complications leading to ICU admission.

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