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Causes of Deaths in an Oncologic Intensive Care Unit: a Clinical and Pathological Study of 34 Autopsies

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Abstract—*We reviewed the charts of the cancer patients admitted in a medical oncology ICU during an 11-month period. Among 330 admissions (55% for a medical complication, 45% for monitoring during administration of an intensive or potentially toxic treatment), 49 patients died and 34 autopsies were performed. Every autopsied case was reviewed by a group of oncologists and pathologists. The direct cause of death was neoplasia itself in only four patients. Six deaths remained unexplained after post mortem examination. In 23.5% of cases, the direct cause of death was a major infection (four aspergillosis, two candidemia, one CMV pneumonia, one acute cholicystitis). Overall, the clinical diagnosis of the immediate cause of death was correct in only 41% of the cases.*

Lesions of pulmonary edema (PE) were found at autopsy in 68% of the cases. No predictive factors for PE were determined.

INTRODUCTION

No study analyzing the causes of death in cancer patients admitted to an intensive care unit has been published so far. Cancer represents today a major lethal disease in industrialized countries. If it is essential to obtain new therapeutic modalities against cancer itself, it is not less important to prevent, diagnose and treat the multiple complications secondary to the neoplastic disease or its therapy. Our group has reported earlier the experience acquired in an intensive care unit (ICU) within a medical oncology department [1]. In this kind of ICU, patients are admitted for two main reasons: a medical complication related or not to their cancer, or the administration under strict monitoring of an intensive and/or potentially toxic treatment.

We retrospectively analyzed the causes of death of the patients admitted over an 11-month period in order to determine the role of autopsy as a retrospective diagnostic tool.

MATERIALS AND METHODS

Patients

Patients included in the present study were those admitted to the medical intensive care unit during an 11-month period from November 1985 to October 1986. There were 330 admissions: 180 (55%) for a medical complication and 150 (45%) for monitoring and/or administration of an intensive and/or potentially toxic treatment. The type of underlying disease—cancer in 96% of the cases—is shown in Table 1. Intensive treatments included phase I cytostatic agents administration (nine patients), infusions of water-insoluble drug contained in liposomes (23 patients), chemotherapy in high risk patients (11 patients) and intraperitoneal chemotherapy (97 cases). Only one patient died in this group during his stay in the ICU. The types of medical complications requiring admission in the ICU are shown in Table 2. Forty-eight of these patients died (27%) and a total of 49 deaths were observed for the whole series (15%).

Methods

Charts and autopsy data of the dead patients were reviewed. Of the 49 deaths, 34 were autopsied. The autopsy contained a complete macroscopic and microscopic analysis of every organ. Special colorations (including silver methylamine for yeast) were performed. Pulmonary edema (PE) was defined by a congestion of the interstitial capillaries, associated with interstitial and alveolar edema and with the presence of fibrinous deposits on the alveolar wall with some hyaline membranes.

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Table 1. *Underlying disease*

	Type of admission			
	Medical complication		Intensive treatment	
	Total number of patients	Number of deaths	Total number of patients	Number of deaths
Solid tumors				
Central nervous system tumor	1	—	—	—
Head and neck cancer	14	2	7	—
Thyroid gland cancer	3	1	2	—
Small cell lung cancer	7	2	9	—
Non-small cell lung cancer	30	16	11	—
Breast cancer	46	10	12	—
Esophageal cancer	4	1	—	—
Colon cancer	4	—	—	—
Anal cancer	1	—	4	—
Renal cancer	2	—	1	—
Prostatic cancer	2	1	—	—
Testis cancer	1	—	—	—
Ovarian cancer	4	—	85	—
Endometrial cancer	1	—	—	—
Cervix cancer	5	2	1	—
Vagina/vulva cancer	5	2	1	—
Soft tissue tumor	3	1	6	—
Bone tumors	2	—	—	—
Melanoma	2	1	5	—
Adenocarcinoma of unknown origin	1	—	—	—
Skin cancer	1	—	—	—
Mesothelioma	—	—	5	—
Subtotal:	138 (77%)	37 (27%)	148	—
Hematological malignancies				
Hodgkin's disease	3	2	—	—
Non-Hodgkin's lymphoma	8	1	—	—
Dysmyelopotetic syndrome	2	1	—	—
Myeloproliferative syndrome	4	1	—	—
Chronic myeloid leukemia acutisation	1	—	1	1
Acute lymphoblastic leukemia	2	—	—	—
Acute non-lymphoblastic leukemia	11	5	1	—
Multiple myeloma	4	1	—	—
Subtotal:	35 (19%)	10 (28%)	2	1
Non-neoplastic diseases:	7 (4%)	1	—	—

For every case a complete clinical report was retrospectively established, including the characteristics of the patient (age, sex, etc.), the neoplastic and underlying diseases, a precise physical status at the time of admission in the ICU, the daily evolution, every treatment received (antineoplastic drugs, antimicrobial therapy, cardiotonic drugs, etc.), any relevant modification of blood parameters, the results of microbiological samples, the records of complementary investigations (X-rays, radionuclide scans, ultrasound, etc.) and the possible cause of death. Every case was discussed between pathologists and medical oncologists and the data of the autopsy were compared to the clinical report. The statistical analysis was performed with the chi-squared test.

RESULTS

Thirty-four patients were evaluable for this study. Table 3 shows a comparison between the clinical direct causes of death and those found at autopsy. Six deaths remained unexplained after the autopsy. We clinically suspected cardiac arythmia in one case, carbonarcosis in two, pulmonary embolism in one. In two cases, we had no explanation.

In three patients for whom the immediate cause of death was not clinically evident, *post mortem* examination revealed respectively cardiac tamponade, diffuse leukemia, and cytomegalovirus (CMV) pneumonia. In eight cases (23.5% of the series), autopsy showed as direct cause of death a major infection (four aspergillosis, two candidemia, one CMV pneumonia and one acute cholecystitis). Only

Table 2. Type of medical complications requiring admission in the ICU

	Number of patients	Number of deaths
Thromboembolic disease	9	1
Cardiac arrhythmia	13	1
Cardiac failure	4	1
Myocardial infarction	3	1
Thoracic pain	5	—
Pericardial disease	5	2
Pleural effusion	7	1
Pneumothorax	1	1
Superior vena cava syndrome	1	—
Pneumonia	4	3
Diffuse pneumonitis	4	2
ARDS	4	2
Other respiratory failures	15	6
Severe fungal disease	6	4
Bacteremia	3	1
Septic shock	6	2
Hypovolemic shock	6	1
Various shocks	7	2
Digestive bleeding	2	1
Acute renal failure	2	1
Hypercalcemia	34	7
Acute abdomen	5	1
Ascitis	1	—
Diffuse encephalopathy	2	1
Infectious meningitis	1	1
Meningeal carcinomatosis	2	—
Intracranial hypertension	4	1
Convulsions	6	—
Paralytic syndrome	5	—
Drug intoxication	5	—
Malignant hypertension	1	—
Syncope	2	—
Lactic acidosis	1	1
Cardiac arrest	4	4
	180	48 (27%)

two of these infections (one aspergillosis and one candidemia) had been suspected *pre mortem* to be the cause of death. Two patients who died from pulmonary aspergillosis had been thought to have died from proximal digestive hemorrhage. Three patients died from acute internal bleeding that was not diagnosed. Cancer has directly caused the death of four patients only. Overall the diagnosis of the direct (immediate) cause of death was correct in 14 cases (41%).

A high frequency of non-cardiac pulmonary edema (PE) was found at autopsy. If PE was recognized as the direct cause of death in seven cases only, we observed anatomical lesions of PE in 68% (23/34) of the patients. We compared the characteristics of the autopsied patients according to the presence or absence of PE lesions (Tables 4a and 4b). We tried to propose some predictive factors of the risk to develop PE among all clinical data, but the statistical evaluation showed no significant difference for each parameter between both groups.

DISCUSSION

All deaths (except one) occurred among the patients admitted for a medical complication in the ICU and not for intensive treatment and/or monitoring. In fact, in only 12% of the cases (4/34) was the direct cause of death cancer itself. Most frequently, the immediate cause of death was a complication of the malignant disease or its treatment. The rate of fatal infection found in our study (23.5%) is in accordance with the results of other investigators analyzing the causes of deaths in an oncology unit [2, 3] as well as in a general hospital [4].

Performing a correct clinical diagnosis of the direct cause of death is usually difficult in such critically ill patients. The possibility of performing extensive diagnostic procedures is often limited, and sophisticated imagery or functional tests are often not applicable. Moreover, because of the expected short-term survival of patients with advanced cancer, uncomfortable investigations (like fiberoptic bronchoscopy) are sometimes not performed. All these reasons may explain why a correct diagnosis was clinically made in only 41% (14/34) of the cases. Other authors already noted similar discrepancies

Table 3. Immediate causes of death revealed by autopsy

Cause of death revealed by autopsy	*n*	*Pre mortem* correct clinical diagnosis	*Pre mortem* incorrect clinical diagnosis
Disseminated neoplasia	4	2	2
Major infection	8	2	6
Non-cardiac pulmonary edema	7	4	3
Acute hemorrhage	3	0	3
Pulmonary embolism	2	2	0
Cerebral stroke	1	1	0
Tamponade	1	0	1
Myocardial infarct	1	0	1
Multifactorial respiratory insufficiency	1	1	0
Unknown	6	2	4

Table 4a. Pulmonary edema according to patient characteristics

	Pulmonary edema	No pulmonary edema
Number	23	11
Mean age (range)	60 (31–75)	56 (31–75)
Sex ratio M/F	15/8	7/4
Type of tumor		
hematological malignancy	8	1
solid tumor	14	10
no tumor	1	0
Extension of cancer		
localized	2	1
metastatic	20	10
Type of antineoplastic treatment		
palliative	10	10
curative	6	0
experimental	2	1
no treatment	5	0
Prior pulmonary radiotherapy	6 (26%)	3 (27%)
Proven infection	9 (39%)	6 (55%)
bacterial	2	2
mycotic	6	4
viral	1	0
Leucopenia at time of death (WBC < 1000/μl)	5 (22%)	3 (27%)
Median duration of stay in ICU (days)	6	5
range	1–21	1–18

*Table 4b. Main critical care procedures and therapies**

	Pulmonary edema	No pulmonary edema
Number	23	11
Artificial ventilation	5	1
(median duration in days)	(6)	(2)
Corticosteroids	10	6
Cardiotonic drugs	9	7
Antimicrobial agents	11	9
Antineoplastic chemotherapy	6	6

*Except medication given during resuscitation.

between *ante mortem* and *post mortem* diagnosis [3–5]. As emphasized by Goldman [4, 6], it is interesting to keep in mind the fact that the percentage of cases with undiagnosed primary causes of death has not diminished between 1912 and today among the overall population. Fortunately constant medical progress allows us to find out and to manage more effectively many previously missed fatal diseases (like bacterial pneumonia, hepatic cirrhosis, etc.) but a longer expectation of life and more recent intensive therapies are responsible for the emergence of new or obscure diseases (like fungal systemic infections, acute hemorrhage due to antineoplastic chemotherapy-induced thrombopenia, etc.). It is thus always interesting to obtain systematic autopsy.

The high frequency of PE found at autopsy in our study is an unreported phenomenon in cancer patients. Many factors might explain this observation. Lungs of cancer patients often suffer from multiple aggressions [7]. Cytostatic drugs like bleomycin are well known to produce diffuse pulmonary lesions. Pulmonary irradiation may be responsible for PE, the long-term effect being fibrosis. Infections often play also an important role, either directly or via endotoxinemia and septic shock [7]. The disturbed immune system of the cancer patient may contribute to the occurrence of PE. In his study on the interaction between invasive tumor cells and the extracellular matrix, Liotta showed that neoplastic cells have the capacity to degrade vascular basement membranes [8]. This destruction of capillaries could explain the hypersensitivity to endotoxin and tumor necrosis factor (or cachectin) demonstrated in animal models [9]. Immune reactions against cancer may also play a role in the occurrence of PE. New immunotherapies have been associated with severe adult respiratory distress syndrome (ARDS), defined as an acute diffuse alteration in lung structure and function with severe hypoxemia [10]. For example, manipulation of the immunologic response to adoptive immunotherapy with interleukin-2 and lymphokine activated killer cells can result in a life-threatening capillary leak syndrome [11–13]. The high risk for cancer patients to develop lesions of PE could thus be due to an enhanced immune response working on pulmonary

capillaries sensitized by the metastatic process. It would be useful to have predictive factors to develop PE. As shown in Tables 4a and 4b, our study did not permit us to find the nature of such parameters. In the past, other studies [14, 15] also failed to determine predictive variables. As recently demonstrated by Artigas [16], there is a strong relationship between the quantity of predisposing conditions and the incidence of PE. Cancer patients often accumulate many of these predisposing factors.

Anyway, our present study contains only a small number of patients, perhaps explaining why statistical analysis is not conclusive. Further clinical studies, including other autopsies but also prospective *in vivo* investigations are required to increase the understanding of these observations.

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