Intensive Care Med (2010) 36:232–240
DOI 10.1007/s00134-009-1709-8

ORIGINAL

Stéphane Legriel
Hélène Marijon
Michael Darmon
Virginie Lemiale
Jean-Pierre Bedos
Benoît Schlemmer
Elie Azoulay

Central neurological complications in critically ill patients with malignancies

Received: 22 April 2009
Accepted: 16 September 2009
Published online: 12 November 2009

This article is discussed in the editorial available at:
doi:10.1007/s00134-009-1713-z.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-009-1709-8) contains supplementary material, which is available to authorized users.

S. Legriel · H. Marijon · M. Darmon · V. Lemiale · J.-P. Bedos · B. Schlemmer · E. Azoulay
Medical Intensive Care Unit, AP-HP, Hôpital Saint-Louis, 75010 Paris, France
e-mail: stlegriel@invivo.edu

S. Legriel · H. Marijon · M. Darmon · V. Lemiale · J.-P. Bedos · B. Schlemmer · E. Azoulay
UFR de Médecine, University Paris-7 Paris-Diderot, 75010 Paris, France

E. Azoulay (✉)
Service de Réanimation Médicale, Hôpital Saint-Louis et Université Paris 7, 1 rue Claude Vellefaux, 75010 Paris, France
e-mail: elie.azoulay@sls.ap-hop-paris.fr
Tel.: +33-1-42499421
Fax: +33-1-42499426

Abstract *Objective:* To determine outcomes in critically ill patients hospitalized in the ICU for central neurological complications of cancer. *Design and setting:* A 7-year retrospective study. *Subject and intervention:* Observational study in 100 critically ill cancer patients with central neurological complications managed using standardized diagnostic and therapeutic strategies. *Measurements and results:* There were 52 men and 48 women, aged 55 years (IQR, 40–65). Presenting manifestations were coma (56%), epilepsy (48%), focal signs (35%), encephalopathy (31%), and meningitis (7%). Cerebral imaging was abnormal in 61 patients, lumbar puncture in 17, and electroencephalography in 6. Neurosurgical biopsy was performed on four patients. The main etiologies included drug toxicity in 28, malignant brain infiltration in 21 patients, and cerebrovascular disease in 20. Mechanical ventilation was needed for 60 patients. Anticancer chemotherapy was administered during the ICU stay in 15 patients. ICU and hospital mortalities were 28 and 45%, respectively. By multivariate analysis, independent positive predictors of hospital mortality were poor performance status [odds ratio (OR) 2.94, 95% CI, 1.01–8.55, $P = 0.047$), focal signs at presentation (OR 3.52, 95% CI, 1.14–10.88, $P = 0.029$), abnormal lumbar puncture (OR 5.49, 95% CI 1.09–27.66, $P = 0.038$), and need for vasoactive drugs (OR 6.47, 95% CI 1.32–31.66, $P = 0.021$), whereas remission of the malignancy (OR 0.20, 95% CI 0.04–0.88, $P = 0.033$) and GCS score at admission (OR 0.81/point, 95% CI, 0.70–0.95, $P = 0.009$) were negative predictors of hospital mortality. *Conclusion:* In cancer patients, central neurological events are mainly related to malignant brain infiltration and drug-related toxicity. Despite advanced severity, a standardized intensive management strategy yields a 55% hospital survival rate.

Keywords Leukemia · Lymphoma · Bone marrow transplantation · Mechanical ventilation · ICU · Cancer

Introduction

Neurological complications are common life-threatening events in patients with malignancies [1, 2]. These may include infiltration of the nervous system or meninges with malignant cells, infections, vascular disorders, and metabolic disturbances indirectly related to the malignancy, treatments, and paraneoplastic syndromes [3, 4].

Central nervous system (CNS) involvement requiring admission to the intensive care unit (ICU) has been

reported in up to 20% of critically ill patients with malignancies [1, 5, 6]. However, there are no studies specifically designed to determine the causes and outcomes of neurological events in this population. The few studies of neurological events in cancer patients outside the ICU focused on patients with bone marrow transplantation [2], specific malignancies [5], or specific patterns of complications [6, 7]. A recent study of 361 patients with hematopoietic stem cell transplantation showed a 16% rate of central neurological events, which were distributed evenly between direct and indirect causes [2]. Hospital mortality was 32% [2].

Recent survival gains in patients treated for solid tumors or hematological malignancies have been ascribed to better understanding and management of organ dysfunctions [8–12]. Given the paucity of information on CNS involvement in critically ill patients with cancer, we conducted a retrospective study of consecutive cancer patients admitted to an ICU with central neurological events. Our objective was to obtain information on the nature and outcomes of neurological events in critically ill cancer patients.

Patients and methods

The ethics committee of the French Society for Critical Care approved this noninterventional retrospective study. We included consecutive patients with hematological malignancies or solid tumors who were admitted to our medical ICU with central neurological complications between January 2000 and December 2007.

Neurological failure was defined by any neurological disorder of central origin among impairment of consciousness, seizure with or without status epilepticus, focal sign, encephalopathy, and meningeal symptoms, which required intensive care management for monitoring or life support management. Coma was defined by the absence of arousal and consciousness, and characterized by a Glasgow Coma Scale (GCS) <9. Encephalopathy was defined by a variable combination of confusion, behavioral abnormalities, an altered level of consciousness, and evidence of either focal or diffuse neurological signs or symptoms.

A standardized form was used to collect the variables listed in Tables 1 and 2. Patient status was considered as remission when no evidence of malignancy could be detected with appropriate explorations during follow-up, regardless of the type of cancer. Patient performance status before hospitalization was categorized in a four-step staging based on health status over the last 3 months (Table E1) [13].

Patient management and ICU admission criteria were identical throughout the study period. The physical examination at admission routinely included a thorough neurological evaluation, with determination of the GCS score [14, 15]. Computed tomography (CT) or magnetic resonance imaging (MRI) was obtained routinely. In patients with no obvious diagnosis within hours from ICU admission, intermittent EEG monitoring and lumbar puncture were also done routinely. Cerebrospinal fluid

Table 1 Patient characteristics and univariate predictors of hospital mortality

No. (%) or median (interquartile range)	All patients ($n = 100$)	Survivors ($n = 55$)	Nonsurvivors ($n = 45$)	OR	95% CI	*P* value
Patient characteristics						
Age (years)	55 (40–65)	55 (36–67)	55 (42–62)	1.00	0.98–1.03	0.78
Female gender	52 (52%)	27 (49%)	25 (56%)	0.77	0.35–1.70	0.52
Poor performance status[a]	44 (44%)	17 (31%)	27 (60%)	3.35	1.46–7.66	**0.004**
Characteristics of the underlying malignancy						
Hematological malignancy (as opposed to solid tumors)	74 (74%)	41 (75%)	33 (73%)	0.94	0.28–2.30	0.89
Newly diagnosed malignancy	16 (16%)	9 (16%)	7 (16%)	1.06	0.36–3.12	0.91
Time since diagnosis (days)	311 (60–952)	320 (67–1,165)	223 (31–936)	1.00	1.00–1.00	0.67
Neutropenia	23 (23%)	12 (22%)	11 (24%)	1.16	0.24–2.95	0.75
Bone marrow or stem cell transplantation	23 (23%)	12 (22%)	11 (24%)	0.79	0.50–1.24	0.30
Autologous	9 (9%)	3 (5%)	6 (13%)	2.53	0.58–10.86	0.21
Allogeneic	14 (14%)	9 (16%)	5 (11%)	0.70	0.21–2.29	0.55
Complete remission	22 (22%)	17 (31%)	5 (11%)	0.28	0.94–0.83	**0.02**
Severity scores at ICU admission						
SAPS II score	55 (43–67)	48 (38–59)	62 (47–74)	1.04	1.01–1.06	**0.001**
LOD score	6 (4–9)	6 (3–8)	7 (5–10)	1.16	1.03–1.30	**0.01**
GCS score	7 (3–10)	8 (5–12)	6 (3–9)	0.88	0.79–0.98	**0.02**

Values in bold are significant ($P < 0.05$)
Higher scores indicate a higher risk of hospital death
ICU intensive care unit, *OR* odds ratio, *95% CI* 95% confidence interval, *SAPS* Simplified Acute Physiology score [37], *LOD* Logistic Organ Dysfunction score [38], *GCS* Glasgow Coma Scale score [14, 15]
[a] Defined as a performance status scale of 3 or 4 [13]

Table 2 Patient characteristics and univariate predictors of hospital mortality

No. (%) or median (interquartile range)	All patients ($n = 100$)	Survivors ($n = 55$)	Nonsurvivors ($n = 45$)	OR	95% CI	*P* value
Reason for neurological admission (one or more)						
Coma	56 (56%)	27 (49%)	29 (64%)	1.88	0.83–4.21	0.12
Status epilepticus	36 (36%)	17 (31%)	19 (43%)	1.69	0.74–3.88	0.21
Focal sign at presentation	35 (35%)	15 (27%)	20 (44%)	2.13	0.92–4.92	0.07
Encephalopathy	31 (31%)	17 (31%)	14 (31%)	1.01	0.43–2.36	0.98
Seizure without status epilepticus	12 (12%)	11 (20%)	1 (2%)	0.09	0.01–0.74	**0.02**
Meningeal symptoms	7 (7%)	3 (5%)	4 (9%)	1.69	0.36–7.98	0.51
Investigations in the ICU						
Abnormal lumbar puncture ($n = 46$)	17 (37%)	6 (11%)	11 (24%)	2.64	0.89–7.83	0.08
Time from neurological impairment onset to etiological diagnosis (days)	1 (0–4)	0 (0–2)	1 (0–5)	1.01	0.98–1.03	0.17
Cause of neurological manifestations (one or more)						
Direct CNS involvement						
Malignant brain infiltration	21 (21%)	10 (18%)	11 (24%)	1.45	0.55–3.82	0.44
Metastases	12 (12%)	5 (9%)	7 (16%)	1.84	0.54–6.25	0.33
Indirect CNS involvement						
Central nervous system injury	56 (56%)	26 (47%)	30 (67%)	2.23	0.98–5.04	0.05
Drug-related[a]	28 (28%)	20 (36%)	8 (18%)	0.37	0.15–0.97	**0.04**
Vascular[b]	20 (20%)	9 (16%)	11 (24%)	1.65	0.62–4.43	0.32
Metabolic[c]	17 (17%)	10 (18%)	7 (16%)	0.83	0.28–2.38	0.73
Central nervous system infection[d]	9 (9%)	3 (6%)	6 (13%)	2.61	0.61–11.12	0.19
Undetermined	13 (13%)	7 (13%)	6 (13%)	1.05	0.33–3.39	0.92
Treatments in the ICU						
Mechanical ventilation	60 (60%)	26 (47%)	34 (76%)	3.33	1.40–7.90	**0.006**
Duration of mechanical ventilation (days)	4 (2–9)	3 (2–5)	6 (3–12)	1.24	1.06–1.45	**0.008**
Vasoactive agents	15 (15%)	3 (5%)	12 (27%)	6.30	1.65–24.03	**0.007**
Anticancer chemotherapy	15 (15%)	7 (13%)	8 (18%)	1.48	0.49–4.46	0.48

Values in bold are significant ($P < 0.05$)
Higher scores indicate a higher risk of hospital death
OR odds ratio, *95% CI* 95% confidence interval

[a] Drug-related CNS involvement including anticancer medication complications ($n = 15$): methotrexate ($n = 4$), cytarabine ($n = 4$), cyclosporine A ($n = 2$), L asparaginase ($n = 1$), sunitinib ($n = 1$), vincristine ($n = 1$), diméthylsulfoxyde ($n = 1$), tacrolimus ($n = 1$); other medication adverse effects ($n = 11$): opioid ($n = 7$), benzodiazepin ($n = 2$), insuline ($n = 1$), malocide ($n = 1$); acute voluntary poisoning ($n = 2$): benzodiazepin ($n = 1$), tricyclic antidepressant ($n = 1$)

[b] Cerebral hemorrhage ($n = 13$): intracerebral hematoma ($n = 8$), subarachnoid hemorrhage ($n = 4$), subdural hematoma ($n = 1$); cerebral infarction ($n = 12$): ischemic stroke ($n = 9$), cerebral thrombophlebitis ($n = 3$)

[c] Diabetic ketoacidosis ($n = 3$), hypernatremia ($n = 3$), hyperuremia related to acute renal failure ($n = 2$), hypoglycemia ($n = 2$), hyperammonemia ($n = 1$), hypocalcemia ($n = 1$), hypophosphoremia ($n = 1$),hypomagnesemia ($n = 1$), hypokalemia ($n = 1$), hypercalcemia ($n = 1$), diabetic hyperglycemic hyperosmolar syndrome ($n = 1$)

[d] Bacteria ($n = 4$): *Pseudomonas aeruginosa* subdural empyema, *Mycobacterium tuberculosis* meningitis, *Streptococcus constellatus* meningitis and subdural empyema, *Listeria monocytogenes* rhombencephalitis; yeasts ($n = 2$): cerebral aspergillosis, cerebral toxoplasmosis; viruses ($n = 1$): herpes simplex viruses 1 meningo-encephalitis, and decapitated meningo-encephalitis

(CSF) abnormalities were defined as a cell count >5/µl, protein >45 mg/dl, glucose <0.5 blood glucose, organisms, and/or atypical cells [16]. Seizure activity on the EEG was defined as continuous or recurrent rhythmic focal or generalized spikes, sharp waves, spike waves, or rhythmic waves changing in amplitude, frequency, and/or spatial distribution [17]. Status epilepticus was diagnosed in patients with continuous clinical seizure activity lasting more than 10 min [18] or, in patients without clinical seizures, as EEG seizure activity lasting more than 30 min [19]. Cerebral MRI and/or CT abnormalities were described as focal and/or diffuse, and as transient or permanent abnormalities. Plasma anticonvulsant drug assays and qualitative tests for toxic substances or medications associated with coma were performed as indicated by the clinical history. Laboratory tests were obtained routinely to look for metabolic abnormalities associated with neurological findings, such as disturbances in serum sodium, calcium, urea, or glucose. Blood cell counts and coagulation tests were done to assess the bleeding risk. Neurosurgical biopsy was performed when focal lesions visualized by cerebral imaging studies remained of unknown or doubtful nature despite a full set of investigations (Fig. 1).

Mechanical ventilation was used according to standardized criteria in patients whose GCS score remained less than 9 despite etiological treatment when a reversible cause was suspected (e.g., status epilepticus or opioid or benzodiazepine overdose). On-scene intubation was required in some of the comatose patients. Finally,

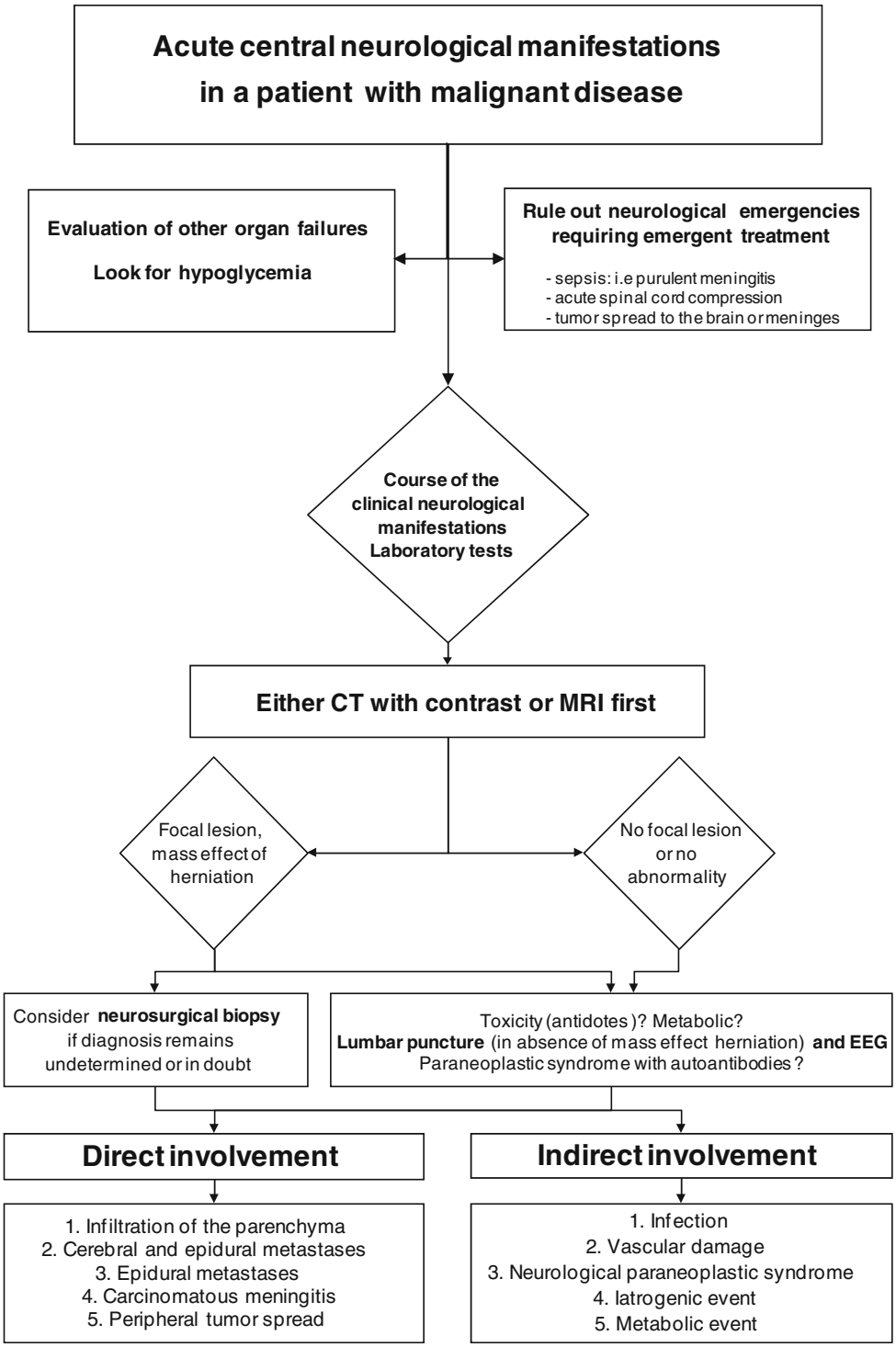

Fig. 1 Diagnostic strategy in cancer patients with acute central neurological manifestations

intubation was also required in some of the patients with actual or impending aspiration pneumonia and respiratory failure or shock [20]. Vasoactive drugs were restricted to patients who had hypotension despite fluid resuscitation or cardiac failure documented by echocardiography and evidence of another organ failure (i.e., oliguria, renal failure, or lactic acidosis). Renal replacement therapy was used according to previously published criteria [21]. Standard medical treatment for the suspected cause was introduced immediately after the initial clinical evaluation (e.g., antimicrobials, anticonvulsants, or antidotes).

Etiological diagnoses were defined as follows. Drug-related neurological complications were defined as adverse neurological events occurring after medical treatment known to induce neurological toxicity. Patients may present with a combination of coma, acute encephalopathy, mood and behavioral disturbances, headaches, seizures, dementia-like episodes, visual disorders, cortical blindness, myelopathy, extrapyramidal syndrome, cerebellar syndrome, meningeal syndrome, and peripheral neuropathy. Only central neurological events were retained in this study. CNS infiltration by a hematological malignancy was diagnosed in patients with at least two of the following criteria: positive autopsy or biopsy, typical neuroradiological images, atypical cells identified by cytology and/or histopathology in marrow smears or bone biopsies, and neuroradiological and clinical response to specific chemotherapy. In patients with unknown solid tumors, CNS metastasis was diagnosed when neuroimaging studies showed a new brain lesion and results were positive from cytological and/or tumor-marker studies. In patients with known solid tumor, this diagnosis was also retained in cases of typical metastatic disease on brain imaging. Cerebrovascular disease was diagnosed based on neuroimaging evidence of acute ischemic or hemorrhagic stroke, cerebral venous thrombosis, or subarachnoid hemorrhage. CNS injury induced by metabolic disturbances was considered when neuroimaging and CSF studies were normal and laboratory tests showed metabolic disturbances. Finally, CNS infection was diagnosed in patients with clinical evidence of sepsis, and positive serological and/or microbiological tests on CSF. Etiologies were categorized using an empirical classification as direct or indirect involvement of the CNS by the malignancy [22, 23]. Thus, malignant brain infiltration and metastases where considered as direct involvement of the CNS, whereas drug-related, vascular, metabolic, CNS infection and injury were considered as indirect involvement of the CNS.

Statistical analysis

Quantitative parameters are reported as median and interquartile range (IQR, 25th–75th percentile) and qualitative parameters as numbers and percentage. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney *U* test or the Wilcoxon test, as appropriate.

Vital status at hospital discharge was known for all study patients. Associations between patient characteristics and hospital mortality were assessed using a logistic regression model. Multivariable analysis was performed using stepwise forward selection to introduce variables whose *P* values were smaller than 0.20 by univariate analysis. Then, the absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked. Variables were tested for colinearity and interactions before inclusion in the multivariable model. Goodness of fit was evaluated by the Hosmer–Lemeshow statistic. The area under the ROC curve was estimated by the statistic c (Association of Predicted Probabilities and Observed Responses). Odds ratios (OR) and their 95% confidence intervals (95% CI) were computed. *P* values less than 0.05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC).

Results

Tables 1 and 2 report the main characteristics of the 100 study patients. Sixteen (16%) patients were managed at the diagnosis phase of the malignancy. Hematological malignancies were present in 74 (74%) patients. Numbers of autologous and allogeneic stem-cell recipients were 9 (9%) and 14 (14%), respectively. A history of anticancer chemotherapy within 4 weeks before ICU admission was noted in 62 patients (Table E2), and neutropenia was found at ICU admission in 23 (23%) patients. Finally, 22 (22%) patients were in remission of their malignancy.

ICU admission occurred at a median of 5 (IQR, 0–13) days after hospital admission and 0 (0–4) days after the onset of the neurological manifestations. There were 16 (16%) patients with previously known epilepsy. Seizure activity was inaugural in 11 (91%) of the 12 patients with simple seizure and 27 (75%) of the 36 patients with status epilepticus. Neuroimaging findings were abnormal in 61 (61%) patients. EEG revealed evidence of non-convulsive status epilepticus in 6 of the 61 (10%) patients who underwent this investigation, and CSF was abnormal in 17 of the 46 (37%) patients who underwent lumbar puncture. Encountered CSF abnormalities were as follows: cell count 67 (18–193)/µl, protein 120 (70–180) mg/dl, and glucose 2.9 (1.6–4.7) mmol/l. Microbiological investigations identified microorganisms reported in Table 2. Abnormal cells revealed carcinomatous meningitis in four patients and blasts in five patients. The three other patients presented with isolated pleiocytosis.

A neurosurgical biopsy was performed in 4 (4%) patients and consistently provided the diagnosis (three cases of primary B-cell lymphoma and one case of primary T-cell lymphoma). Overall, the diagnosis was achieved 1 (0–4) day after neurological symptom onset, but remained undetermined in 13 (13%) patients in whom biopsy was not performed because of the absence of evidence of focal lesion at cerebral imaging, because some of them quickly died or because central neurological signs disappeared rapidly in the remaining patients. Among patients with an etiological diagnosis, 33 (37%) had direct and 74 (85%) indirect CNS involvement.

Mechanical ventilation was needed in 60 (60%) patients for 4 (2–9) days. Vasoactive agents were used in 15 (15%) patients and renal replacement therapy in 6 (6%). The median number of organ failures was of 3 (2–4), resulting in a median LODs score of 6 (4–9). Fifteen (15%) patients received anticancer chemotherapy during the ICU stay (Table E3). Anticancer therapy was implemented in the ICU when the malignancy was directly responsible for organ dysfunction (i.e., compression, mass effect, tumor lysis syndrome).

Mean and median lengths of stay were 7 and 4 (IQR, 3–8) days in the ICU, and 33 and 25 (IQR, 12–44) days in the hospital, respectively. ICU and hospital mortality rates were 28 and 45%, respectively. Among the 16 patients who died within the first week after ICU admission, 8 died within 3 days (3 died at day 1, 2 at day 2, and 3 at day 3). During ICU stay, decisions to withhold or withdraw life-sustaining therapies were implemented in 27 patients. These decisions were based on the finding of carcinomatous meningitis in four patients and to irreversible medical conditions in the remaining patients. One year after ICU admission, mortality rate reached up to 67%.

The results of the univariate analysis are reported in Tables 1 and 2. Independent predictors of hospital mortality are reported in Table 3. Among them, poor performance status defined as Performance Status Scale 3 or 4 (OR 2.94, 95% CI 1.01–8.55, $P = 0.047$), focal signs at presentation (OR 3.52, 95% CI 1.14–10.88, $P = 0.029$), abnormal lumbar puncture (OR 5.49, 95% CI 1.09–27.66, $P = 0.038$), and need for vasoactive drugs (OR 6.47, 95% CI 1.32–31.66, $P = 0.021$) were identified as positives predictors of hospital mortality, whereas remission of the malignancy (OR 0.20, 95% CI 0.04–0.88, $P = 0.033$) and GCS score at admission (OR 0.81/point, 95% CI 0.70–0.95, $P = 0.009$) were negative predictors of hospital mortality.

Discussion

This is the first study reporting the causes and outcomes of central neurological events in critically ill patients with malignancies. A coma was present at ICU admission in more than half of the patients, and 60 (60%) required mechanical ventilation. Most of the patients had indirect CNS involvement, which was often related to medications (28%) or cerebrovascular disease (20%). Direct CNS involvement by the malignancy was noted in only one-third of the patients.

Neurological failure has been reported in about 20% of cancer patients admitted to the ICU [1, 24, 25]. Outside the critical care setting, a few descriptive studies of neurological events in cancer patients have been published [3, 4, 26, 27], but they supply little information about outcomes [28]. We obtained such information in 100 consecutive patients who were managed in a standardized manner. The 45% hospital mortality rate in these patients with at least two organ dysfunctions and high rates of mechanical ventilation and vasoactive drug therapy are in agreement with recent advances in the survival of cancer patients admitted to the ICU [11, 29]. The 1-year mortality rate of 67% after ICU admission was in the same proportion as that of critically ill cancer patients admitted with non-neurological complications [9, 30].

Our population was clinically heterogeneous. Thus, the patients differed regarding the diagnosis (solid tumors or hematological malignancy), time in the course of their disease, history of hematopoietic stem cell transplantation, and presence of neutropenia. Whereas 22% of patients were in remission of their malignancy, 15% required anticancer chemotherapy in the ICU. This heterogeneity improved our ability to identify risk factors for death.

As we previously described, administration of anticancer chemotherapy in the intensive care unit is feasible in cases of advanced disease at cancer diagnosis

Table 3 Multivariate analysis: independent predictors of hospital mortality

	Odds ratio	95% CI	*P* value
Poor performance status (3 or 4)	2.94	1.01–8.55	**0.047**
Remission of the malignancy	0.20	0.04–0.88	**0.033**
Glasgow Coma Scale score at ICU admission	0.81[a]	0.70–0.95	**0.009**
Focal sign at presentation	3.52	1.14–10.88	**0.029**
Abnormal CSF	5.49	1.09–27.66	**0.038**
Need for vasoactive drugs	6.47	1.32–31.66	**0.021**
Time from neurological impairment onset to etiological diagnosis (days)	1.02[b]	0.99–1.05	0.144

Values in bold are significant ($P < 0.05$)

Goodness of fit (Hosmer–Lemeshow) chi-square P value = 0.51

Area under the ROC curve estimated by the statistic c = 0.834

The following variables were entered in the model: poor performance status, remission of the malignancy, Glasgow Coma Scale score at ICU admission, LOD score, focal sign at presentation, time from neurological impairment onset to ICU hospitalization (days), and time from neurological impairment onset to etiological diagnosis (days), abnormal CSF, and need for vasoactive agents

95% CI 95% confidence interval, *ICU* intensive care unit, *CSF* cerebrospinal fluid

[a] Per point, [b] per day

responsible for organ failures [30]. In our cohort, this strategy allowed 50% hospital survival in patients with newly diagnosed cancer presenting with neurological complications. Similarly, 23% of patients experienced neutropenia at ICU admission because of recent anticancer chemotherapy that was no longer associated with poor outcome [31].

A diagnosis was established in 87% of cases, early etiological treatment was combined with supportive care in 66% of patients, and 55% of patients survived to hospital discharge. In a large study of critically ill patients with neurological failure but no malignant disease, hospital mortality was 18% [32]. However, in studies of critically ill cancer patients, hospital mortality was about 60% [1, 24]. In agreement with previous studies, in critically ill patients with cancer, remission at admission and poor performance status were independent predictors of hospital mortality [10, 33]. Focal signs at admission, degree of consciousness, and abnormal CSF also predicted mortality. These easily assessed clinical factors should be recorded routinely for cancer patients with CNS events. Finally, organ dysfunctions in addition to the neurological impairment were associated with hospital mortality. These results may help clinicians to identify patients who are most likely to benefit from aggressive diagnostic and therapeutic management.

Our study has several limitations. First, a corollary of the single-center and retrospective design is uncertainty about the extent to which our population represents the full spectrum of neurological failures in patients with cancer managed in the ICU. For example, in the SOAP study, which focused on patients with infection in the ICU, cancer patients requiring admission because of neurological failure were more likely to have solid tumors than hematological malignancies [34]. However, the large number of cancer patients managed in our hospital and the spectrum of malignant diseases included in the study argue in favor of the representativeness of our population and suggest that our results may apply to other ICUs. Second, this study may not provide the actual picture of severe CNS involvement in cancer patients since we cannot ensure that hematologists and oncologists were always calling intensivists in similar situations. However, from the intensive care perspective, patient management and ICU-admission criteria were identical throughout the study period. Third, the cause of neurological failure escaped diagnosis in 13% of patients. In our study, seizures were present in 48% of patients at admission and coma in 56%. Although only 61% of patients had an EEG, it is reasonable to assume that all patients with persistent coma had an EEG to look for nonconvulsive status epilepticus, a potentially reversible condition whose MRI manifestations may mimic structural damage from a tumor [35]. CSF examination was performed in only 46% of patients, although CSF abnormalities independently predicted hospital mortality. However, CSF examination was probably widely performed in patients with no diagnosis by other investigations. Furthermore, our strategy for managing cancer patients with central neurological manifestations provided the diagnosis in 87% of patients, and there was no excess mortality in the patients who had no diagnosis. A neurosurgical biopsy was performed in only 4% of patients and consistently provided the diagnosis. However, reserving neurosurgical biopsy for patients whose diagnosis remains in doubt despite multiple investigations is standard practice. This practice may deserve reappraisal. Fourth, the time from the onset of neurological manifestations to ICU admission was short in our study. However, most of the patients were admitted after spending several days in a ward without neurological manifestations. As previously reported, earlier ICU admission of cancer patients with critical illnesses requires effective collaboration between intensivists and hematologists or oncologists as well as training of physicians in the identification of ICU admission criteria before the organ failures become irreversible [36]. The Glasgow Coma Scale score, an independent predictor of hospital mortality in our study, should be among the criteria used routinely by hematologists and oncologists to decrease the time to ICU admission (Fig. 1). Fifth, conversely to previous reports, our results highlight the impact of remission of the malignancy on survival. We do believe that in other studies characteristics of the underlying malignancy were not associated with survival since hematologists and oncologists themselves performed the first triage of patients with advanced disease, no lifespan expanding therapy, or with poor chronic health status. However, in this study, the malignanacy involved the CNS in some patients. In this last case, only chemotherapy for cancer can provide survival. However, before ICU admission, assessing the sensitivity to chemotherapy is impossible. Therefore, our finding that the malignancy was associated with outcomes is only the sign that some of the patients did not respond to chemotherapy and died. Finally, even if mortality is an interesting judgement criterion in this population, the retrospective design of the study did not allow assessing functional outcome, which would have been of interest.

In summary, for cancer patients with CNS involvement, a standardized management strategy including multiple diagnostic investigations and early life-sustaining treatment provided a 55% hospital survival rate despite the presence of at least two organ dysfunctions in addition to a hematological malignancy or solid tumor. Hospital mortality was associated with poor performance status and lack of control of the malignancy, the nature and severity of the neurological impairment, and the associated organ dysfunctions. These results invite further studies assessing the impact on survival of earlier and more aggressive diagnostic management.

Acknowledgments The authors thank Antoinette Wolfe, MD, for helping to prepare the manuscript. Presented in part at the 36th Congress of the French Society for Critical Care (2008), Paris, France.

Conflicts of interest statement The authors have no conflict of interest.

References

1. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA (2003) Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. Crit Care Med 31:104–112
2. Denier C, Bourhis JH, Lacroix C, Koscielny S, Bosq J, Sigal R, Said G, Adams D (2006) Spectrum and prognosis of neurologic complications after hematopoietic transplantation. Neurology 67:1990–1997
3. Wen PY, Schiff D (2003) Neurologic complications of solid tumors. Neurol Clin 21:107–140 viii
4. Recht L, Mrugala M (2003) Neurologic complications of hematologic neoplasms. Neurol Clin 21:87–105
5. Seute T, Leffers P, ten Velde GP, Twijnstra A (2004) Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. Cancer 100:801–806
6. Taccone FS, Jeangette SM, Blecic SA (2008) First-ever stroke as initial presentation of systemic cancer. J Stroke Cerebrovasc Dis 17:169–174
7. Safdieh JE, Mead PA, Sepkowitz KA, Kiehn TE, Abrey LE (2008) Bacterial and fungal meningitis in patients with cancer. Neurology 70:943–947
8. Azoulay E, Schlemmer B (2006) Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 32:808–822
9. Darmon M, Thiery G, Ciroldi M, Porcher R, Schlemmer B, Azoulay E (2007) Should dialysis be offered to cancer patients with acute kidney injury? Intensive Care Med 33:765–772
10. Soares M, Salluh JI, Carvalho MS, Darmon M, Rocco JR, Spector N (2006) Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol 24:4003–4010
11. Pene F, Percheron S, Lemiale V, Viallon V, Claessens YE, Marque S, Charpentier J, Angus DC, Cariou A, Chiche JD, Mira JP (2008) Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med 36:690–696
12. Creput C, Galicier L, Buyse S, Azoulay E (2008) Understanding organ dysfunction in hemophagocytic lymphohistiocytosis. Intensive Care Med 34:1177–1187
13. Gotay CC, Kawamoto CT, Bottomley A, Efficace F (2008) The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 26:1355–1363
14. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84
15. Bateman DE (2001) Neurological assessment of coma. J Neurol Neurosurg Psychiatry 71(suppl 1):i13–i17
16. Straus SE, Thorpe KE, Holroyd-Leduc J (2006) How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis? JAMA 296:2012–2022
17. Kaplan PW (2006) The EEG of status epilepticus. J Clin Neurophysiol 23:221–229
18. Chen JW, Wasterlain CG (2006) Status epilepticus: pathophysiology and management in adults. Lancet Neurol 5:246–256
19. Walker M, Cross H, Smith S, Young C, Aicardi J, Appleton R, Aylett S, Besag F, Cock H, DeLorenzo R, Drislane F, Duncan J, Ferrie C, Fujikawa D, Gray W, Kaplan P, Koutroumanidis M, O'Regan M, Plouin P, Sander J, Scott R, Shorvon S, Treiman D, Wasterlain C, Wieshmann U (2005) Non convulsive status epilepticus: Epilepsy Research Foundation workshop reports. Epileptic Disord 7:253–296
20. Stocchetti N, Beretta L, Citerio G (2009) Criteria for extubation in neurologic patients. Crit Care Med 37:1529 author reply 1529–1530
21. Bellomo R, Ronco C (1998) Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney Int Suppl 66:S106–S109
22. Wen PY, Glantz MJ (2003) Neurologic complications of cancer. Preface. Neurol Clin 21:xi–xiii
23. Legriel S, Azoulay E (2009) Life-threatening neurological complications in patients with malignancies yearbook of intensive care and emergency medicine, pp. 828–844
24. Azoulay E, Moreau D, Alberti C, Leleu G, Adrie C, Barboteu M, Cottu P, Levy V, Le Gall JR, Schlemmer B (2000) Predictors of short-term mortality in critically ill patients with solid malignancies. Intensive Care Med 26:1817–1823
25. Staudinger T, Stoiser B, Mullner M, Locker GJ, Laczika K, Knapp S, Burgmann H, Wilfing A, Kofler J, Thalhammer F, Frass M (2000) Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. Crit Care Med 28:1322–1328
26. Plotkin SR, Wen PY (2003) Neurologic complications of cancer therapy. Neurol Clin 21:279–318
27. Sul JK, Deangelis LM (2006) Neurologic complications of cancer chemotherapy. Semin Oncol 33:324–332
28. DeAngelis LM (2001) Brain tumors. N Engl J Med 344:114–123
29. Azoulay E, Alberti C, Bornstain C, Leleu G, Moreau D, Recher C, Chevret S, Le Gall JR, Brochard L, Schlemmer B (2001) Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. Crit Care Med 29:519–525
30. Darmon M, Thiery G, Ciroldi M, de Miranda S, Galicier L, Raffoux E, Le Gall JR, Schlemmer B, Azoulay E (2005) Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. Crit Care Med 33:2488–2493
31. Darmon M, Azoulay E, Alberti C, Fieux F, Moreau D, Le Gall JR, Schlemmer B (2002) Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients. Intensive Care Med 28:1775–1780
32. Broessner G, Helbok R, Lackner P, Mitterberger M, Beer R, Engelhardt K, Brenneis C, Pfausler B, Schmutzhard E (2007) Survival and long-term functional outcome in 1,155 consecutive neurocritical care patients. Crit Care Med 35:2025–2030
33. Peigne V, Rusinova K, Karlin L, Darmon M, Fermand JP, Schlemmer B, Azoulay E (2009) Continued survival gains in recent years among critically ill myeloma patients. Intensive Care Med 35:512–518

34. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL (2009) Characteristics and outcomes of cancer patients in European ICUs. Crit Care 13:R15
35. Hormigo A, Liberato B, Lis E, DeAngelis LM (2004) Nonconvulsive status epilepticus in patients with cancer: imaging abnormalities. Arch Neurol 61:362–365
36. Thiery G, Azoulay E, Darmon M, Ciroldi M, De Miranda S, Levy V, Fieux F, Moreau D, Le Gall JR, Schlemmer B (2005) Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol 23:4406–4413
37. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (saps ii) based on a European/North American multicenter study. JAMA 270:2957–2963
38. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D (1996) The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA 276:802–810