



Clinical features and outcome of patients with primary central nervous system lymphoma admitted to the intensive care unit: a French national expert center experience

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Abstract

Introduction To describe the reasons for intensive care unit (ICU) admission and to evaluate the outcomes and prognostic factors of patients with primary central nervous system lymphoma (PCNSL) admitted to the ICU.

Patients and methods Retrospective observational cohort study of 101 PCNSL patients admitted to 3 ICUs over a two-decade period.

Results Acute respiratory failure, mainly secondary to aspiration pneumonia and *Pneumocystis jirovecii* pneumonia, was the leading reason for ICU admission (33%). Aspiration pneumonia was more common in patients with brainstem tumor (67% vs. 0%, $p < 0.001$), whereas patients with intracranial hypertension were more frequently admitted for coma without seizures (61% vs. 9%, $p = 0.004$). Hospital and 6-month mortality were 47% and 53%, respectively. In multivariate analysis, admission for coma without seizures (OR 7.28), cancer progression (OR 3.47), mechanical ventilation (OR 6.58) and vasopressors (OR 4.07) were associated with higher 6-month mortality. Karnofsky performance status prior to ICU admission was independently associated with lower 6-month mortality (OR 0.96).

Discussion Six-month survival of PCNSL patients admitted to the ICU appears to be relatively favorable (around 50%) and the presence of PCNSL alone is not a relevant criterion for ICU refusal. Predictive factors of mortality may help clinicians to make optimal triage decisions.

Keywords Primary central nervous system lymphoma · Intensive care medicine · Critical care · Neuro-oncology · Prognosis

Introduction

Primary central nervous system lymphoma (PCNSL) is characterized by large B-cell proliferation limited to the central nervous system and the eyes, with no evidence of

concomitant systemic disease [1]. Although PCNSL is a rare cancer that accounts for < 5% of all newly diagnosed primary malignant brain tumors, the incidence of PCNSL is increasing in immunocompetent patients, especially in older people [2–4].

Cancer patients account for 20% of all intensive care unit (ICU) admissions [5, 6, 8] and it has been estimated that 5% of all cancer patients will require ICU admission at some point [2]. Because PCNSL patients are at high risk of life-threatening complications, they present a high probability of ICU admission. Reasons for ICU admission include, but are not limited to, neurological disorders related to the site of the brain tumor (e.g., seizures or coma secondary to intracranial hypertension,) and chemotherapy toxicity, such as acute renal failure [8] and sepsis [9–11].

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Only limited data are currently available concerning the prognosis of PCNSL patients admitted to the ICU. Most data are derived from case series comprising patients with gliomas as well as patients with PCNSL [9, 12, 13]. However, compared to gliomas, especially high-grade gliomas, PCNSL is highly sensitive to chemotherapy [14]. Over recent decades, considerable progress in anticancer therapies [10, 15, 16] has improved the outcome of PCNSL patients [11]. A better understanding of the precipitating factors leading to ICU admission and the determinants of the outcome of PCNSL patients admitted to the ICU could help to improve the quality of triage and management decisions.

The primary objective of our study was to describe the clinical features of PCNSL patients admitted to the ICU, especially by analyzing the reasons for ICU admission. The secondary objective was to assess the hospital mortality and 6-month mortality rates and to identify factors associated with hospital mortality and 6-month mortality. These analyses were conducted on a large cohort of PCNSL patients.

Materials and methods

This retrospective observational multicenter cohort study was carried out from February 1998 to June 2019 in 3 French medical ICUs: a 16-bed ICU in a respiratory department (circa 1200 admissions per year), a 16-bed ICU in a neurology department (circa 300 admissions per year) and a 25-bed ICU in a cardiology department (circa 1000 admissions per year). These 3 ICUs are part of a 1600-bed university hospital with a strong neurological orientation, including a specific neuro-oncology department and the national reference center for PCNSL (i.e., LOC Network) that manages about 40 new patients per year. The study was approved by the French Intensive Care Society Institutional Review Board (CE SRLF 20-15) and patients or their relatives were provided with information about the study. Data from part of this cohort have been previously published [9, 12].

Patient selection

Data were extracted from the ICU database (FusionF, Varimed, France). This database is prospectively managed and comprehensively describes all patient stays. The database of the 3 ICU comprised 25,672 records, corresponding to 100% of admissions over the study period. This set of 25,672 records was retrospectively searched for all consecutive cases of “primary brain tumor” and “non-Hodgkin’s lymphoma” during the study period. After analysis of each selected record, patients meeting the criteria of PCNSL according to the 2016 World Health

Organization Classification of Tumors of the Central Nervous System [17] were included in this study. Patients with previous or concurrent systemic lymphoma, another type of primary malignant brain tumor (e.g., glioma), benign brain tumor, or brain metastases from solid cancers were excluded. Patient who had recently undergone neurosurgery (<2 weeks) or any other type of surgery (<4 weeks) and patients under the age of 18 years were also excluded. For patients with several ICU admissions, only the first ICU stay was included in this analysis.

All patients had histologic (stereotactic brain biopsy) or cytologic (cerebrospinal fluid cytology) confirmation of PCNSL [4, 18].

Data collection

At the time of ICU admission, demographic data such as gender, age, pre-existing immunosuppression and comorbidities according to the Charlson Comorbidity Index [19], physiologic variables such as body temperature, respiratory rate, heart rate, systolic blood pressure and Glasgow coma scale and various laboratory variables were recorded. Neutropenia was defined by a neutrophil count < 0.5 $10^9/L$. Cerebrospinal fluid levels of protein, interleukin (IL)-6 and IL-10 were also recorded. The reason for ICU admission was determined by consensus of two experienced senior intensivists (MD and JM), based on the main symptoms at the time of ICU admission and a set of clinical, laboratory, radiologic and microbiologic features recorded during the ICU stay, as previously reported [9] and detailed in the online supplement. The clinical severity of the patients was assessed by the simplified acute physiology score (SAPS) II [20] and the sequential organ failure assessment (SOFA) score [21]. The functional status was assessed during the week before ICU admission, using the Karnofsky Performance Status Scale [20]. Cancer-related therapies (chemotherapy, brain radiation, and autologous stem cell transplantation) were recorded. The disease status was classified according to international definitions [22] as: (1) newly diagnosed, when the tumor was diagnosed during the four weeks preceding or during the ICU stay and when no anticancer therapy had yet been delivered, (2) complete or partial response, or (3) progression. The site of the brain tumor and the presence of intracranial hypertension on admission were also recorded. Intracranial hypertension was defined as headache or altered level of consciousness associated with cerebral edema, midline shift and/or brain herniation on brain CT-scan or magnetic resonance imaging [23, 24].

Life-sustaining interventions, hospital mortality and mortality 6 months after ICU admission (6-month mortality) were recorded.

Statistical analysis

Data were expressed as number and percentage (n , %) for categorical variables, and as median (0.25–0.75 interquartile interval) for continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test and continuous variables were compared using the Mann–Whitney test. All tests were two-sided, and the significance level was set at 0.05. Multivariate logistic regression was used to identify factors associated with hospital and 6-month mortality, adjusted for all other variables identified by univariate analysis with $p < 0.20$, except for SAPS II, which was redundant with other variables. Missing data were imputed by the nearest neighbor method (1.5%). Odds ratios (ORs) and their 95% confidence intervals were calculated for significant factors. Kaplan–Meier survival curves according to disease status and reason for ICU admission were computed for 6-month mortality. The study period was subdivided into two periods (1998–2008 and 2009–2019) and changes in mortality rates and severity over periods were analyzed using a Chi-square test and a Mann–Whitney test, respectively. All analyses were performed with R software version 3.5.2.

Results

Figure 1 displays the study flow chart. Of the 101 patients included in the study, 71 (70%) were admitted to the respiratory department ICU, 22 (22%) were admitted to the neurological ICU and 8 (8%) were admitted to the cardiology department ICU.

Patient characteristics

The diagnosis of PCNSL was based on stereotactic biopsy in 91 (90%) patients and cytological analysis of cerebrospinal fluid in the remaining 10 (10%) patients. Ninety-seven (97%) patients had diffuse large B-cell lymphoma and the remaining four (4%) patients had T-cell lymphoma. The main characteristics of the 101 patients are displayed in Table 1. Seventeen patients (17%) had pre-existing immunosuppression, 12 (12%) of whom had undergone solid organ transplantation and 5 (5%) of whom had human immunodeficiency virus (HIV) infection. Prior to admission, 82 (82%) patients had received chemotherapy, 14 (14%) had received brain radiotherapy, 11 (11%) had received autologous stem cell transplantation and 84 (84%) had received high-dose corticosteroid therapy. Cerebrospinal fluid protein, IL-6 and IL-10 assays during the 3 months prior to ICU admission were available for 57 (57%), 35 (35%) and 35 (35%) patients, respectively. Median CSF protein was 0.7 (0.5–1.2) g/L, median CSF IL-6 was 6 (3–24) pg/mL and median CSF

IL-10 was 8 (1–42) pg/mL. IL-6 and IL-10 were undetectable in nine (26%) and nine (26%) patients, respectively (not necessarily the same patients). For the 88 (88%) patients in whom the diagnosis of PCNSL was established prior to admission, the median time interval between diagnosis and ICU admission was 4 (1–11) months.

Reasons for ICU admission

Reasons for ICU admission are reported in Table 1. Coma was the main reason for ICU admission (47%). Among the patients admitted for coma, intracranial hypertension was more common in comatose patients without seizures than in comatose patients with seizures (61% vs. 9%, $p = 0.004$). Admission for coma without seizures was more common among patients with newly diagnosed or progressive disease than in patients with complete or partial response (33% vs. 9%, $p = 0.003$).

Acute respiratory failure (ARF) was the second leading reason for ICU admission (32%), mostly secondary to acute infectious pneumonia (27/33 [82%]), with a substantial proportion of cases of aspiration pneumonia (9/27) and *Pneumocystis jirovecii* pneumonia (7/27). More details on the causes of ARF are listed in Table S1 in the Online Supplement. The Glasgow coma scale score on admission was significantly lower in patients with aspiration pneumonia than in patients with other causes of ARF (7 [6–11] vs. 14 [13–15], $p = 0.016$). Brainstem tumor was more frequently observed in patients with aspiration pneumonia than in patients with other causes of ARF (67% vs. 0%, $p < 0.001$).

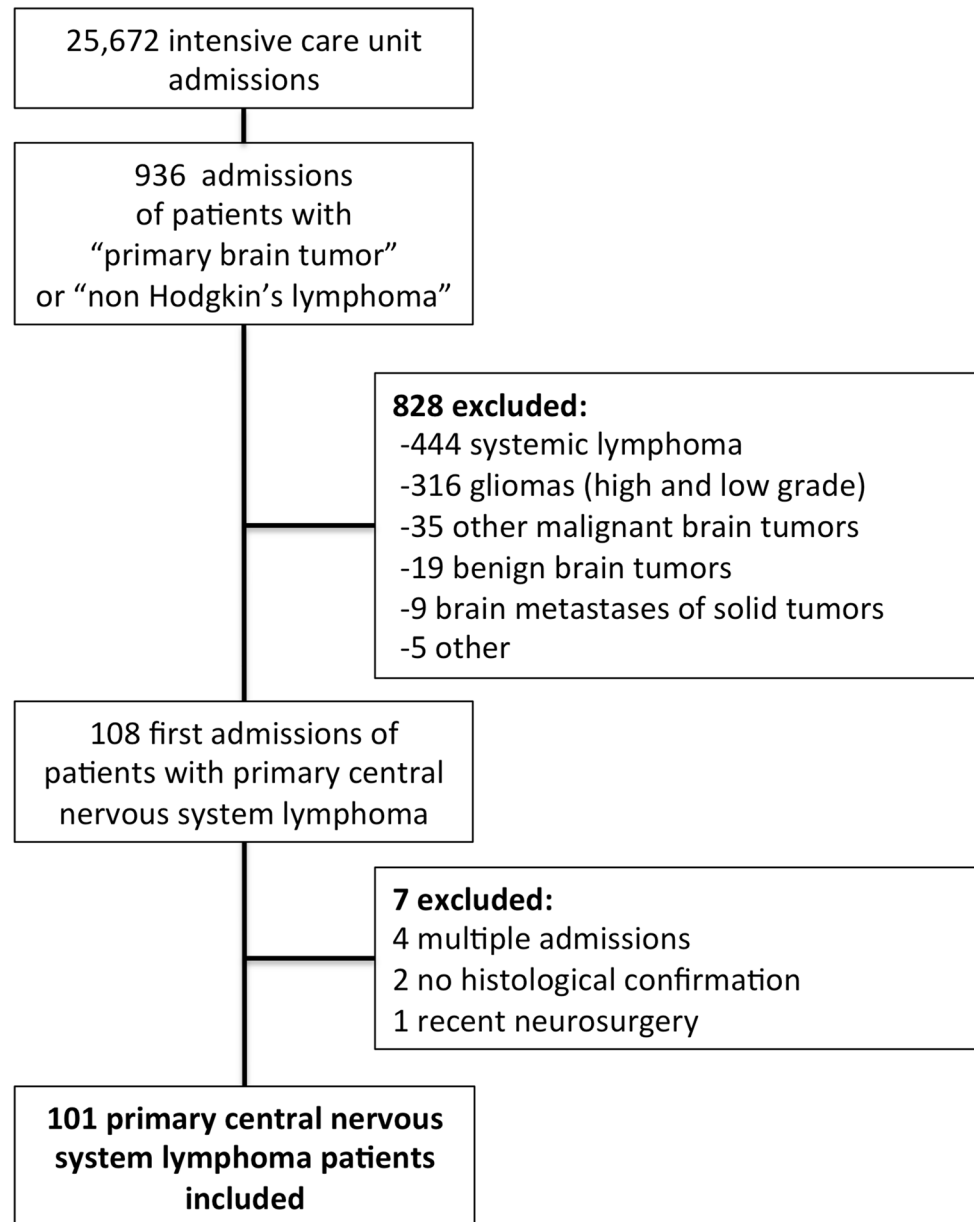
Hospital and 6-month mortality

Intensive care unit, hospital and 6-month mortality were 26%, 47% and 53%, respectively. Hospital mortality, 6-month mortality and SAPS II were not significantly different between the two periods of admission ($p = 0.637$, $p = 0.835$ and $p = 0.785$, respectively). Lengths of ICU and hospital stay were 6 (3–10) days and 19 (8–44) days, respectively.

Table 1 shows the factors associated with hospital mortality identified by univariate analysis. Multivariate logistic regression analysis identified four variables significantly associated with higher hospital mortality: pre-existing immunosuppression (Odds ratio [OR] 5.35, 95% confidence interval [95% CI] 1.07–30.79, $p = 0.047$), Charlson comorbidity index (OR 1.44, 95% CI 1.08–1.99, $p = 0.017$), mechanical ventilation (OR 9.74, 95% CI 3.09–36.15, $p < 0.001$), and vasopressors (OR 4.71, 95% CI 1.41–17.49, $p = 0.015$).

Table 2 shows the factors associated with 6-month mortality identified by univariate analysis. Multivariate logistic regression analysis identified five variables

Fig. 1 Study flow chart



significantly associated with 6-month mortality. Admission for coma without seizures (OR 7.28, 95% CI 1.48–51.40, $p=0.025$), cancer progression (OR 3.47, 95% CI 1.09–12.46, $p=0.042$), mechanical ventilation (OR 6.58, 95% CI 2.13–22.76, $p=0.002$) and vasopressors (OR 4.07, 95% CI 1.16–16.04, $p=0.034$) were associated with higher 6-month mortality, while one factor, Karnofsky performance status prior to ICU admission, was independently associated with lower 6-month mortality (OR 0.96, 95% CI 0.93–0.99, $p=0.027$).

Figure 2 displays the 6-month survival probability according to the reasons for ICU admission and disease status. The highest 6-month survival probability was observed in patients with responsive disease admitted for coma with

seizures or sepsis. More details on Fig. 2 are reported in the Online Supplement.

Discussion

The main results of this study can be summarized as follows. In PCNSL patients admitted to the ICU: (1) ARF, mainly due to aspiration pneumonia, was the leading reason for ICU admission, (2) aspiration pneumonia was associated with the presence of brainstem tumor, (3) medium-term survival was relatively high and (4) admission for coma without seizures, need for life-supporting intervention (mechanical ventilation, vasopressors) and presence of pre-existing

Table 1 Univariate analysis: factors associated with hospital mortality

Variables	Hospital mortality		p value	
	All (n = 101)	Survivors (n = 54)		Non-survivors (n = 47)
Age, years	60 [54–69]	61 [54–70]	60 [53–69]	0.966
Gender (male), n (%)	63 (62)	32 (59)	31 (66)	0.488
Charlson comorbidity index	4 [3–6]	4 [2–5]	4 [3–6]	0.055
Pre-existing immunosuppression, n (%)	17 (17)	5 (9)	12 (26)	0.029
KPS at admission, %	60 [50–70]	70 [60–75]	60 [40–70]	0.021
Disease status at admission				
Progression, n (%)	45 (45)	18 (33)	27 (57)	0.026
Newly diagnosed, n (%)	13 (13)	6 (9)	7 (15)	0.383
Partial/complete response, n (%)	43 (43)	29 (54)	14 (30)	0.015
Tumor site				
Infratentorial site, n (%)	25 (25)	9 (17)	16 (34)	0.044
Brainstem site, n (%)	17 (17)	5 (9)	12 (26)	0.029
Orbital involvement, n (%)	9 (9)	7 (13)	2 (4)	0.170
Intracranial hypertension, n (%)	27 (27)	10 (19)	17 (36)	0.046
Reason for admission				
Acute respiratory failure, n (%)	33 (33)	18 (33)	15 (32)	0.880
Sepsis/Septic shock, n (%)	24 (24)	14 (26)	10 (21)	0.584
Coma without seizures, n (%)	23 (23)	9 (17)	14 (30)	0.117
Coma with seizures, n (%)	11 (10)	7 (13)	4 (9)	0.537
Other, n (%)	10 (10)	6 (11)	4 (8)	0.678
Simplified acute physiology score II	47 [34–60]	42 [30–52]	52 [45–67]	<0.001
Physiological variables at admission				
Glasgow coma scale	13 [7–15]	14 [11–15]	9 [4–13]	<0.001
Heart rate, beats/min	101 [80–117]	97 [81–117]	103 [80–117]	1.000
Systolic blood pressure, mmHg	122 [109–140]	121 [108–137]	124 [110–143]	0.538
Respiratory rate, cycle/min	22 [18–27]	23 [18–28]	22 [18–26]	0.281
Temperature, °C	38 [36–37]	38 [36–38]	37 [36–37]	0.318
Laboratory variables at admission				
Leukocyte count, 10 ⁹ /L	7.1 [0.9–12.4]	6.5 [0.3–11.2]	8.3[1.4–13.3]	0.334
Neutropenia, < 500/mm ³ , n (%)	24 (24)	13 (24)	11 (23)	0.937
Serum creatinine, μmol/L	90 [57–142]	76 [53–108]	107 [66–189]	0.012
Serum lactate dehydrogenase, U/L	497 [378–671]	440 [345–626]	565 [426–778]	0.023
Life-sustaining intervention				
Mechanical ventilation, n (%)	50 (50)	17 (32)	33 (70)	<0.001
Vasopressor, n (%)	30 (30)	9 (17)	21 (45)	0.002
Renal replacement therapy, n (%)	9 (9)	3 (6)	6 (13)	0.297

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables

KPS Karnofsky performance status

immunosuppression were independently associated with mortality. To the best of our knowledge, this is the largest published cohort of PCNSL patients admitted to the ICU.

Comparison with existing data

ARF is the leading reason for ICU admission of cancer patients [25, 26] and is generally related to opportunistic or non-opportunistic lung infections, secondary to neutropenia [27]. In our study, ARF was the leading reason for ICU admission, mainly secondary to acute infectious pneumonia. Due to the association of polychemotherapy and high-dose

corticosteroids used to treat PCNSL, these patients are at increased risk of neutropenia and subsequent infection. Compared to patients with other primary malignant brain tumors [9, 12, 13] or other solid cancers [28, 29], we found a relatively high proportion of patients with neutropenia, similar to that observed in critically ill patients with other systemic hematologic malignancies (e.g., leukaemia, lymphoma, myeloma) [26]. Dysphagia and swallowing dysfunction are also commonly reported in PCNSL patients and in patients with other primary malignant brain tumors [30], predisposing to aspiration and subsequent pneumonia. Finally, we observed a high rate of *Pneumocystis jirovecii*

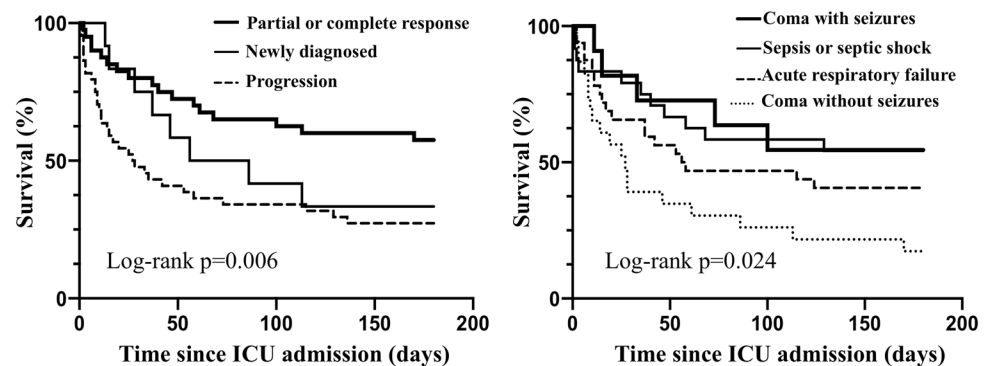
Table 2 Univariate analysis: factors associated with 6-month mortality

Variables	6-month mortality		p value
	Survivors (n = 42)	Non-survivors (n = 59)	
Age, years	60 [53–69]	61 [56–70]	0.372
Gender (male), n (%)	23 (55)	40 (68)	0.183
Charlson comorbidity index	4 [3–6]	4 [3–6]	0.891
Pre-existing immunosuppression, n (%)	4 (10)	13 (22)	0.216
KPS at ICU admission, %	70 [60–80]	60 [50–70]	0.008
Disease status at admission			
Cancer progression, n (%)	12 (29)	33 (56)	0.008
Newly diagnosed, n (%)	5 (12)	8 (14)	0.757
Controlled, n (%)	24 (57)	18 (31)	0.012
Tumor site			
Infratentorial site, n (%)	7 (17)	18 (31)	0.212
Brainstem site, n (%)	4 (10)	13 (22)	0.097
Orbital involvement, n (%)	6 (14)	3 (5)	0.158
Intracranial hypertension n (%)	7 (17)	20 (34)	0.054
Reason for admission			
Acute respiratory failure, n (%)	13 (31)	20 (34)	0.756
Sepsis/Septic shock, n (%)	13 (31)	11 (19)	0.152
Coma without seizures, n (%)	4 (10)	19 (32)	0.008
Coma with seizures, n (%)	6 (14)	5 (8)	0.519
Other, n (%)	6 (14)	4 (7)	0.312
Simplified acute physiology score II	39 [28–50]	52 [43–67]	<0.001
Physiological variables at admission			
Glasgow coma scale	15 [12–15]	10 [6–14]	<0.001
Heart rate, beats/min	90 [79–114]	104 [83–120]	0.201
Systolic blood pressure, mmHg	119 [105–135]	125 [112–143]	0.148
Respiratory rate, cycle/min	22 [18–27]	23 [19–27]	0.956
Temperature, °C	38 [36–38]	37 [36–37]	0.512
Laboratory variables at admission			
Leukocyte count, /mm ³	6.5 [0.5–11.1]	8.0 [1.4–13.7]	0.385
Neutropenia, < 500/mm ³ , n (%)	10 (24)	14 (24)	0.993
Serum creatinine, μmol/L	76 [56–112]	100 [61–169]	0.193
Serum lactate dehydrogenase, U/L	438 [353–573]	563 [405–789]	0.031
Life-sustaining intervention			
Mechanical ventilation, n (%)	11 (26)	39 (66)	<0.001
Vasopressor, n (%)	7 (17)	23 (39)	0.016
Renal replacement therapy, n (%)	3 (7)	6 (10)	0.732

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables

KPS Karnofsky performance status

Fig. 2 Kaplan–Meier survival curves (6-month mortality) according to the reason for intensive care unit (ICU) admission (left panel) and disease status (right panel)



pneumonia, probably related to CD4+ cell-mediated immunosuppression (corticosteroids, brain radiotherapy, methotrexate), as reported in similar settings [31, 32].

Tumor site had an impact on the reasons for ICU admission, as the higher rate of aspiration pneumonia observed in patients with brainstem tumor suggest direct impairment of anatomic structures extending from the brainstem nuclei to nerves innervating laryngeal muscles. The relatively low proportion of ICU admissions for coma with seizures (11%) observed in PCNSL patients, compared to patients with other primary malignant brain tumors, especially gliomas (26–41%) [12, 13], could also be explained by a higher rate of subcortical tumor sites [32–34]. Tumor stage also had an impact on the reasons for ICU admission, as patients with progressive disease were more frequently admitted for coma secondary to intracranial hypertension without seizures (e.g., tumor swelling, perilesional edema, tumor bleeding) or a direct mass-effect on the brainstem (in the case of infratentorial tumor).

Hospital and 6-month mortality observed in PCNSL patients were similar to those observed in patients with other systemic hematologic malignancies [26] or other solid cancers [27, 28, 35, 36], suggesting that, as for other types of cancer, the mere presence of PCNSL does not constitute sufficient reason to deny ICU admission. Because patients with PCNSL have a better prognosis than patients with high-grade glioma [6, 7, 16], we could have expected better survival of PCNSL patients. However, the mortality observed in our study was similar to that observed in series including high-grade glioma patients [13]. Despite the better prognosis of PCNSL compared to high-grade glioma, we did not observe better ICU survival in the PCNSL patients of our series. This could be explained by the lower proportion of admission for seizures in PCNSL compared to gliomas [12]. If the prognosis of comatose patients with seizures admitted to the ICU is generally good [37], in our study, the absence of seizures constituted clearly an independent risk factor for mortality. Indeed, only 17% of patients admitted for coma without seizures are still alive at 6 months vs. 54% when admitted for coma with seizures. This is an important finding in terms of triage decisions for ICU admission in comatose patients, in whom prompt discrimination between seizures or intracranial hypertension as the cause of the coma would avoid futile use of ICU resources. Initiation of mechanical ventilation and use of vasopressors were independent predictors of mortality, confirming numerous reports demonstrating the deleterious impact of mechanical ventilation and vasopressors on the prognosis of ICU patients with hematologic malignancies [26] or solid tumors [25, 34, 35].

Finally, we found that the presence of a pre-existing immunosuppression in PCNSL was a strong predictor of hospital mortality, confirming accumulated evidence that critically ill immunocompromised patients are exposed to

a roughly two-fold increased risk of mortality compared to critically ill immunocompetent patients, especially in the presence of ARF. More specifically, this result is in line with a recent report showing that HIV-positive patients with PCNSL, compared to HIV-negative patients, have a lower probability of complete remission and overall survival [38].

Pictured summary for clinical practice

Based on evidence provided by our results and based on our experience as a national reference center, we thought that a real-life clinical picture-based approach might provide a simple visualization of a kind of hierarchy between typical patients, with higher and lower survival probabilities (Fig. 3). These various scenarios are designed to practically address the most relevant variables to determining the goal of care in a given patient when ICU admission is considered. These relevant variables include: (1) performance status, (2) reasons for ICU admission (seizures or sepsis vs. coma without seizures), (3) number of organ failures (one vs. two or more), (4) disease status (responsive vs. progressive, and also various less quantifiable variables, such as quality of life or patient willingness).

Limitations

The present study has several limitations. First, it was a retrospective study, which involves a potential bias in patient selection or data collection. However, data were extracted from a prospectively managed database and the rarity of the disease remains a major obstacle to prospective studies, even with a multicenter design. Second, although these patients exhibited a relatively high survival probability 6 months after ICU discharge, no information was available concerning their functional status and quality of life, which is likely to be altered in this setting. Third, we did not report any information on possible maintenance of anticancer therapy after ICU discharge, which may influence 6-month survival. Finally, we only considered patients admitted to the ICU. Patients who were not considered for ICU admission for any reason, such as poor prognosis or performance status, were therefore not included in this analysis.

Conclusion

In conclusion, in this study, we report that almost one-half of all PCNSL patients admitted to the ICU were alive 6 months after ICU discharge, suggesting that the simple presence of PCNSL should not preclude patients from the potential benefits of ICU admission. Simple and easily identifiable factors, such as reasons for ICU admission, disease status and Karnofsky performance status at ICU

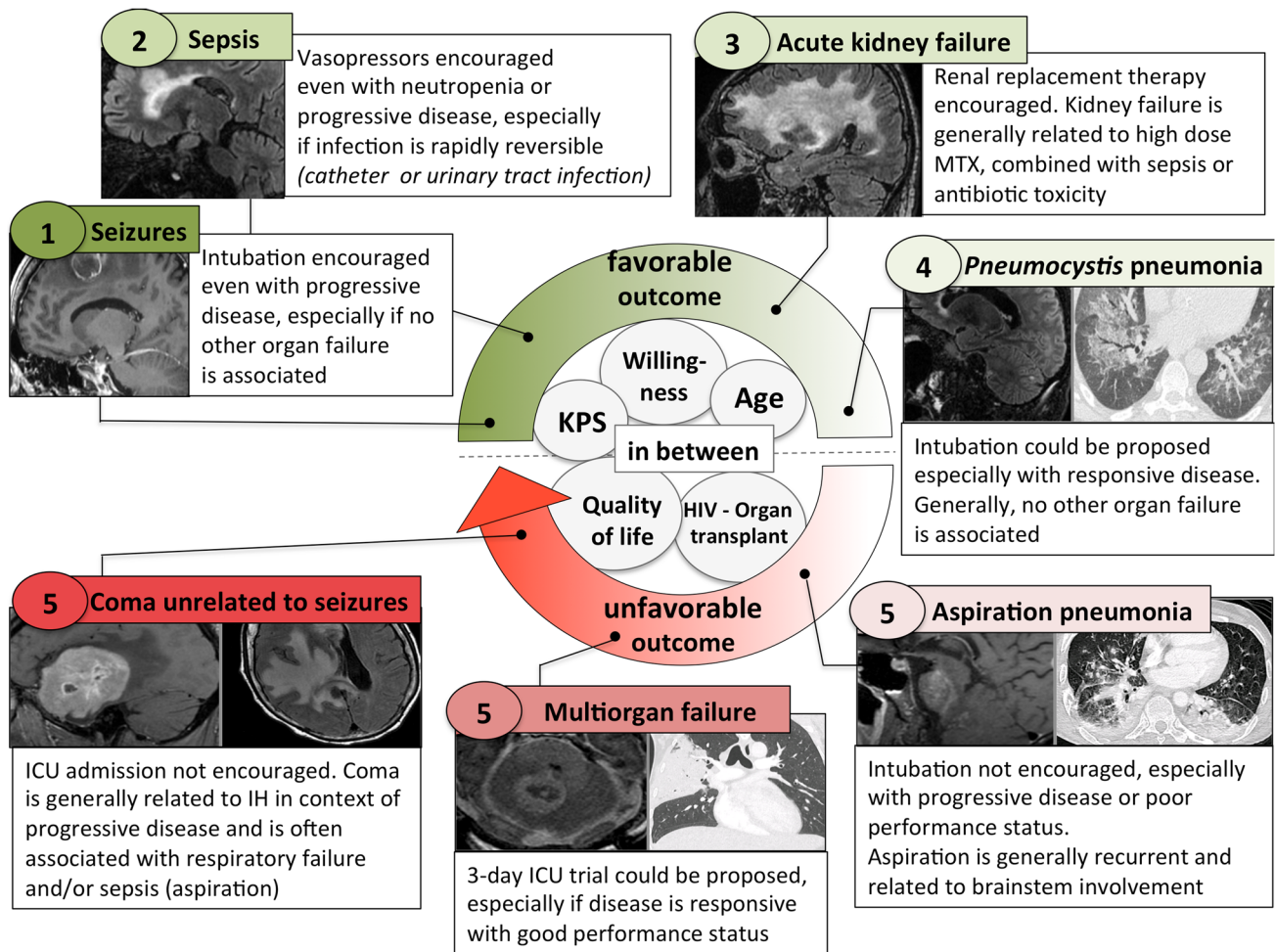


Fig. 3 Experience-based typical clinical situations with which neuro-oncologists and intensivists must be familiar when considering transfer of a primary central nervous system lymphoma patient to the intensive care unit (ICU). These seven scenarios are classified from

the best (scenario 1) to the worst (scenario 7) survival probability after ICU admission. *ICU* intensive care unit, *KPS* Karnofsky performance status, *HIV* human immunodeficiency virus, *IH* intracranial hypertension

admission, are strong independent predictors of medium-term mortality that may help clinicians to optimize triage decisions.

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Author contributions A: conceptualization/methodology. B: analysis/statistics-software. C: data acquisition/curation. D: data interpretation. E: writing original draft. F: approval original draft. Maxens Decavèle: A, B, C, D, E, F. Alénor Dreyfus: A, B, C, D, E, F. Nicolas Gatulle: B, C, D, F. Nicolas Weiss: C, D, F. Isabelle Rivals: A, B, D, F. Caroline Houillier: C, D, E, F. Sophie Demeret: C, D, F. Julien Mayaux: C, D, F. Martin Dres: C, D, F. Elise Morawiec: C, D, F. Julie Delemazure: C, D, F. Sylvain Choquet: C, D, F. Charles-Edouard Luyt: C, D, F. Khe Hoang-Xuan: A, F. Thomas Similowski: A, F. Alexandre Demoule: A, B, C, D, E, F.

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Compliance with ethical standards

Conflicts of interest Thomas Similowski reports personal fees from ADEP Assistance, AstraZeneca France, Boehringer Ingelheim France, Chiesi France, GSK France, Lungpacer Inc., Novartis France, TEVA France, outside the submitted work; In addition, Dr. Similowski has a patent titled “brain-ventilator interface” licensed to Air Liquide Medical Systems and MyBrainTechnology, a patent for a “protection device for intubation” pending, and a patent for a “non-contact thoracic movement imaging system” pending. Alexandre Demoule reports personal fees from Medtronic, grants, personal fees and non-financial support from Philips, personal fees from Baxter, personal fees from Hamilton, personal fees and non-financial support from Fisher and Paykel, grants from French Ministry of Health, personal fees from Getinge, grants and personal fees from Respinor, grants and non-financial support from Lungpacer, outside the submitted work. Martin Dres received personal fees and travel expenses from Lungpacer outside the submitted work. Nicolas Weiss has signed research contracts with Eumedica,

BMS, MedDay pharmaceuticals; he has also received personal fees from Norgine and Alpha-Wasserman and Consultant fees from Med-Day Pharmaceuticals. Ahmed Idbaih reports Ahmed Idbaih reports grants and travel funding from Carthera (September 2019), grants from Transgene, grants from Sanofi, grants from Air Liquide, travel funding from Leo Pharma, grants from Nutritheragene, outside the submitted work. Charles-Edouard Luyt reports having receiving fees from Bayer Healthcare, ThermoFischer Brahms, Biomérieux, Faron, Carmat, Aerogen, Merck Sharp and Dohme, outside the submitted work. Other authors had no conflict of interest to declare.

Ethical approval The study was approved by the French Intensive Care Society Institutional Review Board (CE SRLF 20-15) and information was given to the patients or their relatives.


Availability of data and material Our data are available to ensure transparency.

References

- Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R et al (2015) European association for neuro-oncology task force on primary CNS lymphoma. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. *Lancet Oncol* 16:e322–e332
- Geneviève C, Andrew P, Dominique C, Jonathan S, Hansjakob F, del Julia A et al (2016) Cohort profile: collaboration of observational HIV epidemiological research Europe (COHERE) in EuroCoord. *Int J Epidemiol* 46:797–797
- Shiels MS, Pfeiffer RM, Besson C, Clarke CA, Morton LM, Nogueira L et al (2016) Trends in primary central nervous system lymphoma incidence and survival in the U.S. *Br J Haematol* 174:417–424
- van der Meulen M, Dinmohamed AG, Visser O, Doorduijn JK, Bromberg JEC (2017) Improved survival in primary central nervous system lymphoma up to age 70 only: a population-based study on incidence, primary treatment and survival in The Netherlands, 1989–2015. *Leukemia* 31:1822–1825
- Darmon M, Bourmaud A, Georges Q, Soares M, Jeon K, Oeyen S et al (2019) Changes in critically ill cancer patients' short-term outcome over the last decades: results of systematic review with meta-analysis on individual data. *Intensive Care Med* 45:977–987
- Puxty K, McLoone P, Quasim T, Sloan B, Kinsella J, Morrison DS (2015) Risk of critical illness among patients with solid cancers: a population-based observational study. *JAMA Oncol* 1:1078–1085
- Vincent J-L, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J et al (2014) Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2:380–386
- Valade S, Mariotte E, Azoulay E, Darmon M (2020) High-dose methotrexate in ICU patients: a retrospective study. *Ann Intensive Care* 3(10):81
- Decavèle M, Rivals I, Marois C, Cantier M, Weiss N, Lemasle L et al (2019) Etiology and prognosis of acute respiratory failure in patients with primary malignant brain tumors admitted to the intensive care unit. *J Neurooncol* 142:139–148
- Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B et al (2013) Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 31:3971–3979
- Houillier C, Soussain C, Ghesquière H, Soubeyran P, Chinot O, Taillandier L et al (2020) Management and outcome of primary CNS lymphoma in the modern era: an LOC network study. *Neurology* 94:e1027–e1039
- Decavèle M, Weiss N, Rivals I, Prodanovic H, Idbaih A, Mayaux J et al (2017) Prognosis of patients with primary malignant brain tumors admitted to the intensive care unit: a two-decade experience. *J Neurol* 264:2303–2312
- Tabouret E, Boucard C, Devillier R, Barrie M, Boussen S, Aufran D et al (2016) Neuro-oncological patients admitted in intensive-care unit: predictive factors and functional outcome. *J Neurooncol* 127:111–117
- Cobert J, Hochberg E, Woldenberg N, Hochberg F (2010) Monotherapy with methotrexate for primary central nervous lymphoma has single agent activity in the absence of radiotherapy: a single institution cohort. *J Neurooncol* 98:385–393
- Houillier C, Ghesquière H, Chabrot C, Soussain C, Ahle G, Choquet S et al (2017) Rituximab, methotrexate, procarbazine, vincristine and intensified cytarabine consolidation for primary central nervous system lymphoma (PCNSL) in the elderly: a LOC network study. *J Neurooncol* 133:315–320
- Omuro A, Correa DD, DeAngelis LM, Moskowitz CH, Matasar MJ, Kaley TJ et al (2015) R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood* 125:1403–1410
- Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK et al (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 131:803–820
- Fox CP, Phillips EH, Smith J, Linton K, Gallop-Evans E, Hemmaway C et al (2019) British Society for Haematology. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. *Br J Haematol* 184:348–363
- Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. *J Clin Epidemiol* 47:1245–1251
- Le Gall JR, Lemeshow S, Saulnier FA (1993) New simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 270:2957–2963
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22:707–710
- Schag CC, Heinrich RL, Ganz PA (1984) Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol* 2:187–193
- Kartal MG, Algin O (2014) Evaluation of hydrocephalus and other cerebrospinal fluid disorders with MRI: an update. *Insights Imaging* 5:531–541
- Fernando SM, Tran A, Cheng W, Rochweg B, Taljaard M, Kyere-manteng K et al (2019) Diagnosis of elevated intracranial pressure in critically ill adults: systematic review and meta-analysis. *BMJ* 366:14225
- Azoulay E, Thiéry G, Chevret S, Moreau D, Darmon M, Bergeron A et al (2004) The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine (Baltimore)* 83:360–370
- Azoulay E, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J et al (2013) Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en réanimation oncohématologique study. *J Clin Oncol* 31:2810–2818
- 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
28. Namendys-Silva SA, Texcocano-Becerra J, Herrera-Gómez A (2010) Prognostic factors in critically ill patients with solid tumours admitted to an oncological intensive care unit. *Anaesth Intensive Care* 38:317–324
 29. Soares M, Darmon M, Salluh JI, Ferreira CG, Thiéry G, Schlemmer B et al (2007) Prognosis of lung cancer patients with life-threatening complications. *Chest* 131:840–846
 30. Park DH, Chun MH, Lee SJ, Song YB (2013) Comparison of swallowing functions between brain tumor and stroke patients. *Ann Rehabil Med* 37:633–641
 31. Moradi A, Tajedini A, Mehrabian A, Sadeghi S, Semnani V, Khodabakhshi R et al (2006) Clinicopathological features of primary central nervous system lymphoma. *Neurosciences (Riyadh)* 11:284–288
 32. Mahindra AK, Grossman SA (2003) Pneumocystis carinii pneumonia in HIV negative patients with primary brain tumors. *J Neurooncol* 63:263–270
 33. Fox J, Ajinkya S, Houston P, Lindhorst S, Cachia D, Olar A et al (2019) Seizures in patents with primary central nervous system lymphoma: prevalence and associated features. *J Neurol Sci* 400:34–38
 34. Vecht CJ, Kerkhof M, Duran-Pena A (2014) Seizure prognosis in brain tumors: new insights and evidence-based management. *Oncologist* 19:751–759
 35. Roques S, Parrot A, Lavole A, Ancel PY, Gounant V, Djibre M et al (2009) Six-month prognosis of patients with lung cancer admitted to the intensive care unit. *Intensive Care Med* 35:2044–2050
 36. Soares M, Toffart AC, Timsit JF, Burghi G, Irrazábal C, Pattison N et al (2014) Intensive care in patients with lung cancer: a multinational study. *Ann Oncol* 25:1829–1835
 37. Vooturi S, Jayalakshmi S, Sahu S, Mohandas S (2014) Prognosis and predictors of outcome of refractory generalized convulsive status epilepticus in adults treated in neurointensive care unit. *Clin Neurol Neurosurg* 126:7–10
 38. Bayraktar S, Bayraktar UD, Ramos JC, Stefanovic A, Lossos IS (2011) Primary CNS lymphoma in HIV positive and negative patients: comparison of clinical characteristics, outcome and prognostic factors. *J Neurooncol* 101:257–265

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