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Impact of front line relative dose intensity for methotrexate and comorbidities in immunocompetent elderly patients with primary central nervous system lymphoma

Impact de la dose-intensité relative de méthotrexate et des comorbidités chez les patients âgés immunocompétents traités en première ligne pour un lymphome cérébral primitif

RDI-MTX and comorbidities in elderly with PCNSL

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Liste des abréviations

AraC	Cytarabine
BBB	Blood-brain barrier
CCI	Charlson Comorbidity Index
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CNS	Central nervous system
CR	Complete remission
CSF	Cerebrospinal fluid
DLBCL	Diffuse large B-cell lymphoma
HD-Arac	High-dose cytarabine
HD-MTX	High-dose methotrexate
HIV	Human immunodeficiency virus
HR	Hazard ratio
IELSG	International Extranodal Lymphoma Study Group
KPS	Karnofsky performance status
MGA	Multidimensional geriatric assessment
MSKCC	Memorial Sloan-Kettering Cancer Center
MTX	Methotrexate
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PCNSL	Primary central nervous system lymphoma
PFS	Progression-free survival
RDI	Relative dose intensity
RDI-MTX	Relative dose intensity for methotrexate
95% CI	95% confidence interval

Plan

Impact of front line relative dose intensity for methotrexate and comorbidities in immunocompetent elderly patients with primary central nervous system lymphoma

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RESUME

Background. Primary central nervous system lymphomas (PCNSL) are non-Hodgkin lymphomas strictly localized to the CNS, with specific biology, and which mainly occur in elderly patients with comorbidities. Current treatment in younger patients relies on high-dose methotexate and high-dose cytarabine. The aim of this study was to evaluate the efficacy and feasibility of this treatment in elderly patients and to assess potential prognostic factors associated with survival.

Methods. We conducted a retrospective study in two centers between January 2008 and September 2015 including 35 elderly immunocompetent patients who received first-line treatment with high-dose methotrexate.

Results. With a median follow-up of 19.8 months (range: 1.7 – 73.4 months), median overall survival (OS) was 39.5 months (95% confidence interval (95% CI): 18.3 – 60.7) and median progression-free survival (PFS) was 25.8 months (95% CI: 5.2 – 46.4). In univariate analysis, administration of high-dose cytarabine and achieving a relative dose intensity for methotrexate > 75% were associated with increased OS ($p = 0.006$ and $p = 0.003$, respectively) and PFS ($p = 0.003$ and $p = 0.04$, respectively) whereas a high MSKCC, a PCNSL-specific prognostic score, and comorbidities defined by a CIRS-G score ≥ 8, were associated with decreased OS ($p = 0.02$ and $p = 0.03$, respectively). A CIRS-G score ≥ 8 was also associated with decreased PFS ($p = 0.04$).

Conclusions. Comorbidities and relative dose intensity for methotrexate are important for the prognostic of elderly patients with PCNSL. These results must be confirmed in prospective trials.

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) are non-Hodgkin lymphomas (NHL) strictly localized to the CNS. They represent 3 to 4% of all primary cerebral tumors, about 1% of all lymphomas, and 4 to 6% of all extra-nodal lymphomas (1). Their incidence is constantly increasing in immunocompetent patients (2). In almost 95% of cases, PCNSL are diffuse large B-cell lymphomas (DLBCL) (3), especially of post-germinative center phenotype and EBV negative (4). Increased progress are being made in the understanding of the biology of this specific entity (5).

Treatment mainly relies on drugs capable of crossing the blood-brain barrier (BBB) in order to obtain sufficient cytotoxic concentrations in the cerebrospinal fluid (CSF). High-dose methotrexate (HD-MTX) and high-dose cytarabine (HD-AraC) have this ability and have become the reference treatment in this disease (1).

Fifty percent of patients with PCNSL are elderly patients (≥ 60 years old) (6) with a dismal prognosis in comparison to younger patients. This is probably due to a higher number of comorbidities and to an increased susceptibility to iatrogeny (6,7). The decision process is therefore harder in this specific population with difficulties regarding which patient will be able to tolerate treatment and how to adapt its intensity.

We conducted a retrospective study in order to evaluate the efficacy and feasibility of HD-MTX and to assess potential prognostic factors including the administration of rituximab, HD-AraC, relative dose intensity for methotrexate, and comorbidities in this elderly population.

MÉTHODES

Inclusion Criteria

This is a retrospective study performed in two centers (Angers University Hospital and Le Mans Hospital) between January 2008 and September 2015. Patients were identified through the database of the Pathological Department of Angers University Hospital.

We included immunocompetent patients ≥ 60 years old diagnosed with a histology-proven DLBCL subtype of PCNSL (by stereotactic biopsy or open surgery, all performed and centrally reviewed at Angers University Hospital) who received first-line treatment including at least one infusion of HD-MTX.

Patients with HIV infection or with solid organ transplantation, with secondary CNS involvement or sole ocular lymphoma were excluded. Patients who received no treatment (including steroid therapy only), radiotherapy only or low-dose chemotherapy as part of palliative care, who died of surgical complications without receiving any therapy, or who received treatment in other centers, were not included.

Data Collection

All data were collected from individual patient medical records. Two PCNSL-specific prognostic scores were calculated if all data were available: *International Extranodal Lymphoma Study Group* score (IELSG, combination of 5 variables: age, ECOG performance status, serum LDH level, CSF protein concentration and involvement of deep structures of the brain i.e. basal ganglia and/or corpus callosum and/or brain stem and/or cerebellum) (8) and *Memorial Sloan-Kettering Cancer Center* score (MSKCC, combination of 2 variables: age and Karnofsky performance score) (9). Three geriatric-specific comorbidity scores used in oncology were also calculated according to current guidelines, excluding PCNSL: the *Charlson Comorbidity Index* (CCI) (10), the *Cumulative Illness Rating Scale for Geriatrics* (CIRS-G) (11,12) and the *G8* (13).

Relative dose intensity for methotrexate (RDI-MTX) was calculated for each patient according to the method published by Hryniuk W.M. & Goodyear M. (14). It is the ratio of the actual total dose intensity for MTX and the planned total dose intensity for MTX, expressed as a percentage. Actual total dose intensity is the ratio of the actual total dose for MTX over the real treatment duration, expressed as mg/week. Planned total dose intensity is the ratio of the planned total dose for MTX over the entire planned treatment duration according to a given treatment protocol and expressed as mg/week. Treatment duration was calculated from the first day of the first course of HD-MTX to the 22^{nd} or 29^{th} day of the last course, according to treatment protocol. For patients who stopped treatment due to progression or death, RDI was calculated based on the number of courses actually

completed. For patients who stopped treatment for other reasons (mainly toxicity), treatment duration was calculated based on the planned number of remaining courses with a dose equal to zero. This method allowed to take into account treatment delays, dose reductions, and discontinuation of treatment for reasons other than progression or death.

End Points

Response to treatment was evaluated according to criteria from the *International Primary CNS Lymphoma Collaborative Group* (15). Toxicity was graded according to the *Common Terminology Criteria for Adverse Events Version 4.03* (16). Overall survival (OS) was calculated from the day of the biopsy to the day of death or was censored at last follow-up. Progression-free survival (PFS) was calculated from the day of the biopsy to the day of relapse or death or was censored at last follow-up.

Statistical Analyses

Categorical variables were presented as numbers with proportions and continuous variables were presented as medians with range. Patients characteristics were compared between groups using the Chi-square test or the Fisher's exact test, if appropriate, for categorical variables, and Student's *t*-test for continuous variables. OS and PFS were estimated through the Kaplan-Meier method. Potential prognostic factors for OS and PFS were evaluated by univariate analysis using the log-rank test. A p-value lower than 0.05 was set as statistically significant. Statistical analysis was performed with IBM SPSS Statistics software version 23.0 (IBM Corp. Released 2015. Armonk, N.Y., USA). The study was conducted in accordance to our institutional ethical committee guidelines.

RÉSULTATS

Patient Characteristics

Patient characteristics at diagnosis are summarized in Table 1. Thirty-five patients were included in this study, among which 17 female patients (49%) and 18 male patients (51%). Median age was 70 years old (range: 60 – 83), median ECOG performance status was 1 (range: 0 – 4) and KPS was ≥ 70 in 19 patients (54%). Median MSKCC score was 2 (range: 1 – 2), whereas IELSG score could be calculated in 12 patients (34%) with a median of 3 (range: 2 – 5). Median CCI was 1 (range: 0 – 5) and severe (≥ 2) in 8 patients (23%), whereas median CIRS-G was 8 (range: 2 – 23) with 30 patients (86%) suffering from at least one grade 3 – 4 comorbidity. Twenty-nine patients (83%) had a G8 ≤ 14, suggesting frailty.

Treatment

Four HD-MTX-based protocols were administered to patients during the study period (Table 2). Twelve patients (34%) received MPV-A [17], which consisted of 3 courses (1 course = 28 days) of MTX 3,5 g/m² on days 1 and 15, along with procarbazine 100 mg/m² per day on days 1 to 7 and vincristine 1,4 mg/m² (capped at 2 mg) on days 1 and 15, followed by one course of AraC 3 g/m² on days 1 and 2. Eleven patients (31%) received sequential chemotherapy with HD-MTX (3 g/m² on days 1, 10, 25, 35, 60 and 90) and HD-AraC (2 g/m² on days 11, 36 and 37). Ten patients (29%) received MBVP [18,19], which consisted of 3 courses (1 course = 28 days) of MTX 3 g/m² on days 1 and 15, along with etoposide 100 mg/m² on day 2 and carmustine 100 mg/m² on day 3, followed by one course of AraC 3 g/m² on days 1 and 2. Two patients (6%) were treated according to the LCP88 protocol [18], which consisted of 3 courses (1 course = 21 days) of MTX 3 g/m² on day 1, along with teniposide 100 mg/m² on days 2 and 3 and carmustine 100 mg/m² on day 4, followed by whole-brain radiotherapy. In case of excessive toxicity due to HD-MTX, patients could receive additional infusions of HD-AraC (5 patients, 14%).

For the whole cohort, the median number of received HD-MTX infusions was 6 (range: 2 – 10) for a median RDI-MTX of 78% (range: 19 – 99%) whereas the median number of received HD-AraC infusions was 2 (range: 0 – 12).

Other treatments included rituximab, given at a dose of 375 mg/m² on day 1 of each course (19 patients, 54%, with a median of 4 infusions, range: 1 – 10), mostly after 2013 (16 patients, 84%), intrathecal chemotherapy (8 patients, 23%, with a median of 3.5 injections, range: 3 – 5), and brain radiotherapy (7 patients, 20%, median cumulative dose of 40 Gy, range: 30 – 40) with 6 patients receiving whole-brain radiotherapy and one patient receiving involved-field radiotherapy.

Toxicity

All toxicities retrieved from medical records are summarized in Table 3. Regarding HD-MTX, total infusion dose was reduced in 7 patients (20%) corresponding to 29 infusions out of the 183 administered to the entire cohort (16%): 1 patient (3 infusions) due to renal toxicity, 5 patients (20 infusions) had planned dose reduction due to age, altered performance status, and/or comorbidities, 1 patient (6 infusions) had planned dose reduction due to body surface > 2 m^2. Sixteen patients (46%) experienced significant delay (≥ 7 days [20]) in the administration of HD-MTX corresponding to 20 infusions (11% of all infusions). Reasons for delay were: unknown (6 patients, 10 infusions), infection (4 patients, 4 infusions), renal toxicity (2 patients, 2 infusions), anterior ischemic optic neuropathy (1 patient, 1 infusion), overdrainage of ventriculoperitoneal shunt (1 patient, 1 infusion), ischemic stroke (1 patient, 1 infusion), and patient choice (1 patient, 1 infusion). One HD-MTX infusion was omitted in 4 patients (11%), because of liver toxicity (1), infection (1), myocarditis (1), and for an unknown reason (1). HD-MTX was definitively interrupted in 5 patients (15%) due to renal toxicity (3 patients, 9%), patient choice (1, 3%), and behavioral disorder (1, 3%). Hematological toxicity had no significant impact on treatment schedule.

Eight patients (23%) did not receive HD-AraC, because of an unknown reason (4), early death (1), early progressive disease (1), and because it was not planned in the protocol (2).

Three patients (9%) died because of treatment toxicity: 2 patients due to pulmonary infection and 1 patient due to mesenteric ischemia.

Survival

After first-line treatment, an objective response was observed in 26 patients (74%) including complete remission (CR) in 25 patients (71%) and partial remission in 1 (3%). Seven patients (20%) experienced progressive disease and 2 patients (6%) died before evaluation (Table 2). After a median follow-up of 19.8 months (range: 1.7 – 73.4), median OS (Figure 1A) and PFS (Figure 1B) were 39.5 (95% CI: 18.3 – 60.7) and 25.8 months (95% CI: 5.2 – 46.4), respectively. The 2-year and 5-year OS were 62% (95% CI: 45 – 78) and 39% (95% CI: 18 – 60), respectively. The 2-year and 5-year PFS were 52% (95% CI: 35 – 70) and 25% (95% CI: 6 – 44), respectively.

Prognostic Factors

The following factors were evaluated by univariate analysis: time between the onset of symptoms and diagnosis (< 30 days vs ≥ 30 days), time between diagnosis and start of treatment (< 30 days vs ≥ 30 days), serum albumin (< 35 g/L vs ≥ 35 g/L), MSKCC score (1 vs 2), G8 (≤ 14 vs > 14), CCI (< 2 vs ≥ 2), total CIRS-G (< 8 vs ≥ 8), number of grade 3 – 4 comorbidities according to CIRS-G (0 vs ≥ 1), RDI-MTX (≤ 75% vs > 75%),

administration of rituximab (yes vs no), and administration of HD-AraC (yes vs no). Results are summarized in Table 4.

OS was increased in patients for whom RDI-MTX > 75% could be achieved ($p = 0.003$) (Figure 2A) and in patients who received HD-AraC ($p = 0.006$) (Figure 2B) whereas it was decreased in those who had high MSKCC score ($p = 0.02$) and CIRS-G ($p = 0.03$) (Figure 2C).

PFS was also increased in patients for whom RDI-MTX > 75% could be achieved ($p = 0.04$) (Figure 2D) and in patients who received HD-AraC ($p = 0.003$) (Figure 2E) whereas it was decreased in those who had a high CIRS-G ($p = 0.04$) (Figure 2F).

DISCUSSION ET CONCLUSION

In aggressive NHL, the ability to maintain RDI for chemotherapy has been shown to be an important and independent predictor of CR and survival (21), with thresholds ranging from 75 to 90% (21). In PCNSL, HD-MTX is the most important drug and its efficacy and toxicity relies on its pharmacokinetics and administration schedule. In this indication, it has been shown that HD-MTX should be given at a dose of at least 3 g/m² with an i.v. infusion duration of no longer than 3h, for at least 4 courses with intervals no longer than 3 weeks (22). Until now, only absolute MTX dose intensity has been studied, which does not have impact on survival or toxicity (23). In our study, HD-MTX was administered according to current guidelines, and we are able to show for the first time that RDI-MTX is a prognostic factor for both OS and PFS. We chose a threshold of 75% among others because it was the lower one to have shown prognostic value in systemic DLBCL (21).

Patients who received RDI-MTX ≤ 75% were significantly older than those who achieved a RDI-MTX > 75%, resulting in more upfront HD-MTX dose reduction in this group. Other factors which also could have been related to dose reduction, such as comorbidity scores, did not differ, perhaps because of a lack of power. Given its favorable toxicity profile resulting in few significant treatment delays and few treatment discontinuation, and because upfront HD-MTX dose reduction accounted for most of RDI reduction, it appears that full HD-MTX dose can and should be maintained in elderly patients. Selecting patients able to tolerate such treatment remains a major issue.

HD-AraC is currently the only drug, other than HD-MTX, to have shown a benefit in PCNSL (24). The HD-AraC administration schedules used in our study did not allow us to calculate RDI. Although administration of HD-AraC increased both OS and PFS, it was infused at the end of treatment in 2 out of the 3 protocols using it, mitigating our results. Indeed, disease chemo-refractoriness or early death precluded its administration in some patients.

Rituximab is an anti-CD20 antibody that had revolutionized the treatment and prognosis of systemic NHL (25) even though its use in PCNSL remains a matter of debate (26). Because of its large size (145 kD), its crossing through the BBB is as low as 0 – 4.4% after i.v. administration (27). It is supposed that its maximal efficacy could be attained at the beginning of treatment, when the BBB is disrupted by PCNSL, as shown in an animal model (28). Batchelor et al. (29) were the first to show clinical activity of rituximab in human PCNSL. Twelve patients with refractory/relapsed PCNSL after HD-MTX were treated with weekly i.v. rituximab monotherapy at a dose of 375 mg/m²/infusion, for 8 weeks. Overall response rate was 36%, median PFS was 57 days and median OS was

20.9 months. Rituximab also showed activity in first line setting in a murine model, significantly improving survival whether or not there was concomitant MTX infusion or osmotic BBB disruption (30). Since then, several phase II prospective clinical studies showed encouraging results for the use of rituximab in first line setting (27,31–33), but no reliable conclusion can be drawn because these studies were not randomized. Five retrospective studies have compared the use of rituximab in this setting but with conflicting results (34–38). Heterogeneity regarding treatment protocols, infusion schedules, dose and number of infusions of rituximab across studies and the low number of patients receiving rituximab limit their impact. In our study, rituximab infused at a standard dose according to standard schedule (375 mg/m² on day 1 of each course), did not improve PFS or OS. This may be due to the low number of patients receiving rituximab, and to inappropriate dosing and infusion schedule for PCNSL. Because of passive diffusion (27), a therapeutic CSF concentration may be obtained by increasing dose and/or number of infusions, and eventually by performing them before restoring BBB continuity with HD-MTX.

Most patients with PCNSL are over 60 years old and suffer from comorbidities which interfere with optimal treatment for PCNSL. In addition, treatment can be responsible for decompensation of these comorbidities hence, for morbidity and mortality. Comorbidity scores were developed to evaluate the individual impact of each comorbidity on prognosis in patients with cancer in order to predict tolerance and, in the end, adjust treatment. A recent review of the literature focusing on comorbidities in systemic NHL patients was performed by Terret et al. (39). Among 15 studies, 6 studies found an association between comorbidities and decreased survival, including 3 out of 5 studies evaluating CCI (40–42) and 1 out of 6 studies evaluating CIRS-G (43). Unfortunately, because of extreme heterogeneity between studies in terms of population, treatment and threshold of the scores, it was not possible to draw a reliable conclusion. Another way to identify elderly cancer patients at higher risk of mortality during treatment is to perform a multidimensional geriatric assessment (MGA), which had proven to be useful for predicting toxicity (44,45) and survival (46,47), but is a time- and resource-consuming method. Therefore, the G8 score was developed to rapidly identify patients requiring further geriatric assessment, and was validated in a prospective and multicenter setting (48). In this study, 1435 patients > 70 years old, including 112 (7.8%) patients with NHL, were recruited before any first-line treatment for various cancers. In the whole population, 68.4% of patients showed impaired G8 (defined by a score ≤ 14) and were deemed to require additional evaluation before initiating treatment with a 76.5% sensitivity, a 64.4% specificity and an area under the curve of 0.804 (95% CI: 0.78 – 0.83) compared to the gold-standard (MGA). In multivariate analysis, an impaired G8 was considered as an independent prognostic factor for poorer 1-year OS (HR 2.72; 95% CI: 1.66 – 4.47; $p < 0.0001$). These data were confirmed in a recent review of the literature performed by the *International*

Society of Geriatric Oncology (49) but its universal applicability to all cancer subtypes remains a matter of debate. For instance, an impaired G8 was not predictive for chemotherapy intolerance nor 1-year OS in elderly patients with various hematological malignancies (50). To our knowledge, our study is the first to assess the impact of comorbidities in an elderly population with PCNSL. A CIRS-G ≥ 8 was associated both with decreased OS and PFS. This result must be tempered by the fact that there is no consensual threshold and that it may reflect a more complex reality: increased toxicity of treatment, dose reduction, treatment delays, decompensated comorbidities, palliative care at relapse.

The main limitations of our study are its retrospective nature altering the reliability of our data and necessarily inducing a selection bias, as well as its reduced number of patients, leading to quite a moderate power which precluded more advanced statistical analyses. Indeed, we deliberately chose not to perform a multivariate analysis which would not have been relevant. Because the intentionality of the study was rather to provide clues for future reflection on management of this population, rather than to make definitive conclusions, we also chose not to correct the p-value to take into account the type I error inflation associated with multiple tests, as this would have prevented to highlight some factors.

In conclusion, current frontline HD-MTX-based protocols allow high CR rate and both satisfactory OS and PFS in immunocompetent elderly patients with PCNSL. Our study provides clues for future reflection on optimal management of this population, underlining the importance of achieving a RDI-MTX > 75%, of combining this drug with HD-AraC, and to take comorbidities into account in the choice of treatment, as well as dosing and administration schedule. These results must be confirmed in prospective trials.

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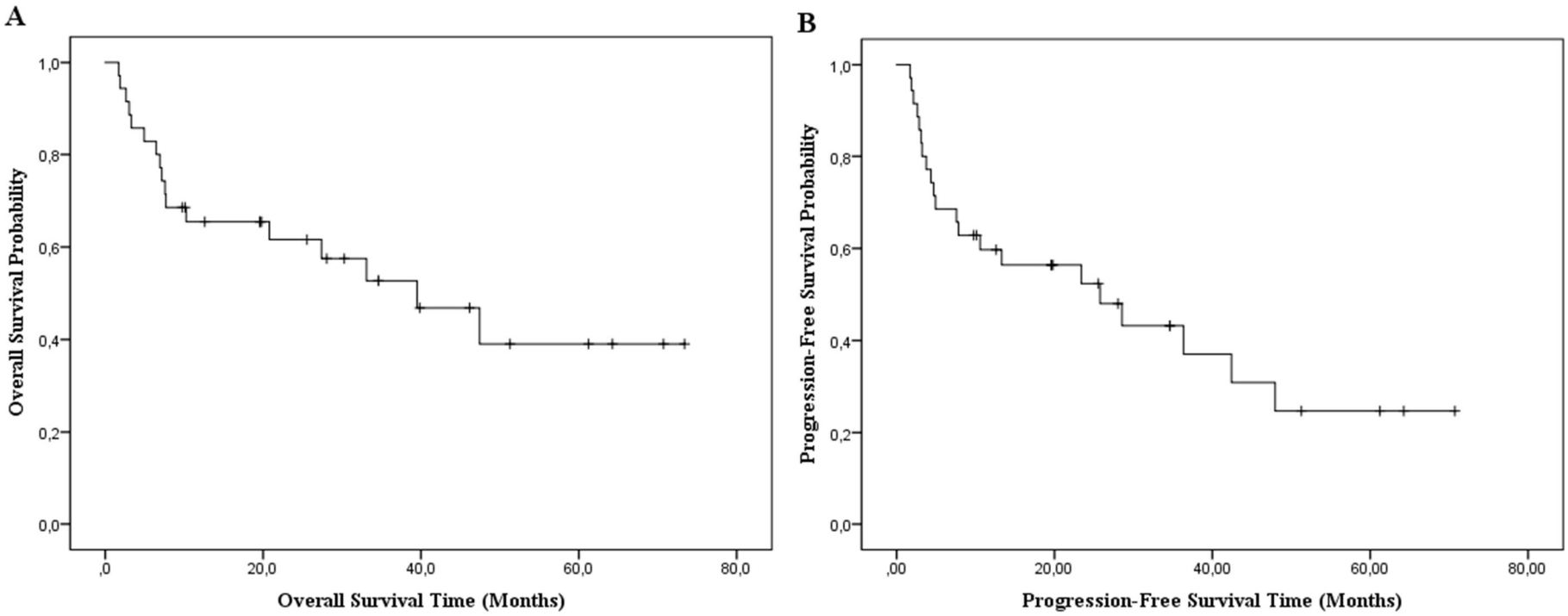

Figure 1. (A) OS for the whole cohort. (B) PFS for the whole cohort.

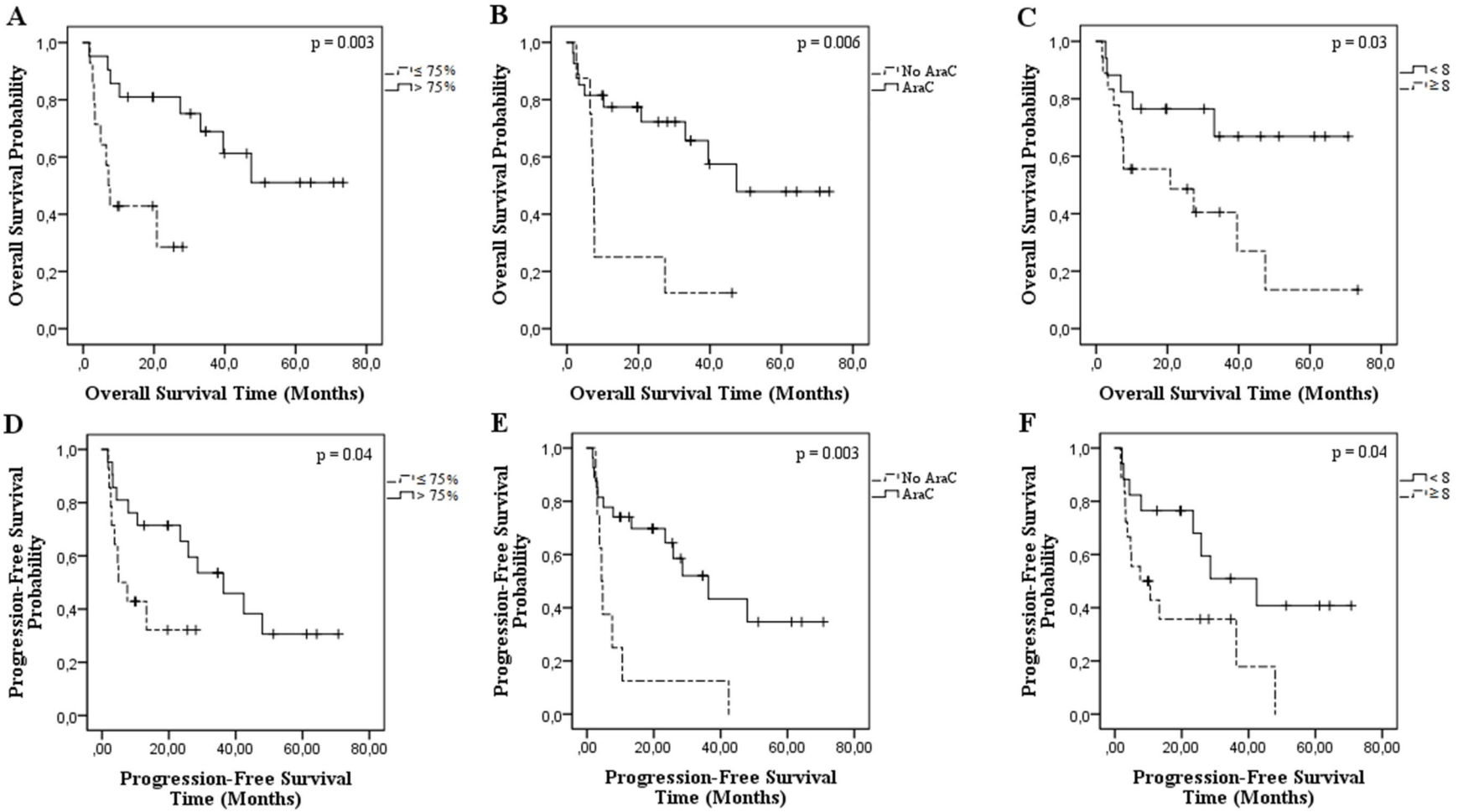

Figure 2. (A) OS according to RDI-MTX. (B) OS according to administration of HD-AraC. (C) OS according to CIRS-G. (D) PFS according to RDI-MTX. (E) PFS according to administration of HD-AraC. (F) PFS according to CIRS-G.

Table 1. Patient characteristics at diagnosis

	All (N = 35)		RDI-MTX > 75% (N = 21)		RDI-MTX ≤ 75% (N = 14)		
Characteristic	N	%	N	%	N	%	p
Median age (years)	70 (60-83)		67 (60-83)		79 (61-83)		**0,02**
Male gender	18	51	11	52	7	50	1
Median ECOG PS	1 (0-4)		1 (0-4)		2 (0-4)		0,1
0 - 1	19	54	12	57	7	50	
2 - 3	13	37	7	33	6	43	
4	3	9	2	10	1	7	
KPS ≥ 70	19	54	12	57	7	50	
Median serum LDH (ratio)	0.86 (0.49-1.85)		0,86 (0,53-1,85)		0,82 (0,49-1,3)		0,67
Elevated	9	26	4	19	5	36	
Median CSF protein concentration (g/L)	0.87 (0.33-1.89)		0,62 (0,51-1,8)		1,12 (0,33-1,89)		0,36
Normal	4	11	2	10	2	14	
Elevated	8	23	3	14	5	36	
Missing	23	66	16	76	7	50	
Localization							
Deep lesions	23	66	12	57	11	79	0,28
Multiple lesions	16	46	8	38	8	57	0,32
Median creatinine clearance according to MDRD (mL/min/1,73 m²)	91 (57-194)		90 (60-152)		98 (57-194)		0,38
< 60 mL/min/1,73 m²	3	9	1	5	2	14	
Median serum albumin (g/L)	34.5 (24-45)		36 (24-45)		30,5 (27-44)		0,14
< 35 g/L	17	49	8	38	9	64	
Missing	1	3	1	5	0	0	
Median IELSG score	3 (2-5)		3 (2-5)		3 (3-5)		0,25
Intermediate	9	25	4	19	5	36	
High	3	9	1	5	2	14	
Missing	23	66	16	76	7	50	
Median MSKCC score	2 (1-2)		1 (1-2)		2 (1-2)		0,3
Class II	17	49	12	57	5	36	
Class III	18	51	9	43	9	64	
Median CCI	1 (0-5)		0 (0-3)		1 (0-5)		0,29
≥ 2	8	23	3	14	5	36	0,22
Median CIRS-G	8 (2-23)		7 (2-14)		12 (4-23)		0,12
≥ 1 grade 3 - 4 comorbidity	30	86	18	86	12	86	1
Median G8	10.5 (5.5-15.5)		11,5 (5,5-15,5)		10,5 (5,5-12,5)		0,15
≤ 14	29	83	15	71	14	100	0,06
Median time between onset of symptoms and diagnosis (days)	37 (6-1056)		24 (6-1056)		46,5 (19-374)		0,7
Median time between diagnosis and start of treatment (days)	18 (3-67)		17 (3-67)		21,5 (8-35)		0,83
Grade 3-4 hematological toxicity	20	57	11	52	9	64	0,73
Grade 3-4 renal toxicity	1	3	0	0	1	7	0,4
Grade 3-4 hepatic toxicity	6	17	4	19	2	14	1
Administration of rituximab	19	54	10	48	9	64	0,49
Administration of HD-AraC	27	77	17	81	10	71	0,69

Table 2. HD-MTX-based protocols and their outcomes

Protocol		Drugs	N	Rituximab	Intrathecal	Radiotherapy	ORR	CR	PR	SD	PD	NE
MPV-A	3 courses of 28 days	MTX 3,5 g/m²/d, D1, D15 + PCB 100 mg/m²/d, D1 - D7 + VCR 1,4 mg/m²/d, D1, D15	12 (34%)	9 (75%)	0	1 (8%)	10 (83%)	10 (83%)	0	0	2 (17%)	0
	then 1 course	AraC 3 g/m²/d, D1, D2										
Sequential		MTX 3 g/m²/d, D1, D10, D25, D35, D60, D90 + AraC 2 g/m²/d, D11, D36, D37	11 (31%)	3 (27%)	0	1 (9%)	5 (45%)	5 (45%)	0	0	4 (37%)	2 (18%)
MBVP	3 courses of 28 days	MTX 3 g/m²/d, D1, D15 + ETO 100 mg/m²/d, D2 + BCNU 100 mg/m²/d, D3	10 (29%)	7 (70%)	6 (60%)	3 (30%)	9 (90%)	8 (80%)	1 (10%)	0	1 (10%)	0
	then 1 course	AraC 2 ou 3 g/m²/d, D1, D2										
LCP88	3 courses of 21 days	MTX 3 g/m²/d, D1 + TENI 100 mg/m²/d, D2, D3 + BCNU 100 mg/m²/d, D4	2 (6%)	0	2 (100%)	2 (100%)	2 (100%)	2 (100%)	0	0	0	0
	then	Whole-brain radiotherapy										
		TOTAL	35 (100%)	19 (54%)	8 (23%)	7 (20%)	26 (74%)	25 (71%)	1 (3%)	0	7 (20%)	2 (6%)

MTX : methotrexate ; PCB : procarbazine ; VCR : vincristine ; AraC : cytarabine ; ETO : etoposide ; BCNU : carmustine ; TENI : teniposide ; ORR : overall response rate ; CR : complete response ; PR : partial response ; SD : stable disease ; PD : progressive disease ; NE : non evaluable

Table 3. Toxicities

Event	Grade I	Grade II	Grade III	Grade IV	Grade V	Total	Median (range)
Neutropenia	2 (6%)	6 (17%)	5 (14%)	10 (29%)	-	23 (66%)	2 (0-4)
Anemia	8 (23%)	16 (46%)	9 (26%)	2 (6%)	-	35 (100%)	2 (1-4)
Thrombopenia	7 (20%)	5 (14%)	5 (14%)	9 (26%)	-	26 (74%)	2 (0-4)
Elevated serum creatinine	9 (26%)	5 (14%)	1 (3%)	0	-	15 (43%)	0 (0-3)
Elevated serum aspartate aminotransferase	7 (20%)	5 (14%)	2 (6%)	0	-	14 (40%)	0 (0-3)
Elevated serum alanine aminotransferase	12 (34%)	4 (12%)	6 (17%)	0	-	22 (63%)	1 (0-3)
Elevated serum alkaline phosphatase	13 (37%)	1 (3%)	0	0	-	14 (40%)	0 (0-2)
Elevated serum total bilirubin	5 (14%)	0	0	0	-	5 (14%)	0 (0-1)
Infection	-	0	9 (26%)	1 (3%)	2 (6%)	12 (35%)	3 (3-5)
Lung	-	0	3 (25%)	0	2 (17%)	5 (14%)	-
Catheter-related	-	0	3 (25%)	0	0	3 (9%)	-
Kidney	-	-	2 (17%)	0	0	2 (6%)	-
Sepsis	-	-	-	1 (8%)	0	1 (3%)	-
Unknown	-	0	1 (8%)	0	0	1 (3%)	-
Myocarditis	0	0	1 (3%)	0	0	1 (3%)	-
Ischemic stroke	0	1 (3%)	0	0	0	1 (3%)	-
Mesenteric ischemia	0	0	0	0	1 (3%)	1 (3%)	-
Anterior ischemic optic neuropathy	0	1 (3%)	0	0	-	1 (3%)	-
Overdrainage of ventriculoperitoneal shunt	0	1 (3%)	0	0	0	1 (3%)	-
Interstitial pneumonitis	0	1 (3%)	0	0	0	1 (3%)	-
Cardiac pulmonary edema	0	0	1 (3%)	0	0	1 (3%)	-

Table 4. Prognostic factors for OS and PFS in univariate analysis

Factor	OS	PFS
	p	p
MSKCC score class II vs class III	0,02	0,11
G8 ≤ 14 vs > 14	0,24	0,42
Serum albumin < 35 g/L vs ≥ 35 g/L	0,34	0,63
Rituximab vs no rituximab	0,73	0,8
Charlson Comorbidity Index < 2 vs ≥ 2	0,8	0,66
Cumulative Illness Rating Scale for Geriatrics		
Total < 8 vs ≥ 8	0,03	0,04
Zero grade 3-4 comorbidity vs ≥ 1	0,62	0,65
Cytarabine vs no cytarabine	0,006	0,003
RDI-MTX ≤ 75% vs > 75%	0,003	0,04
Time between diagnosis and start of treatment < 30 days vs ≥ 30 days	0,37	0,25
Time between onset of symptoms and diagnosis < 30 days vs ≥ 30 days	0,82	0,95

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FARHI Jonathan

Impact de la dose-intensité relative de méthotrexate et des comorbidités chez les patients âgés immunocompétents traités en première ligne pour un lymphome cérébral primitif

RÉSUMÉ

Introduction. Les lymphomes cérébraux primitifs sont des lymphomes non-Hodgkiniens strictement localisés au système nerveux central, à la biologie spécifique et survenant principalement chez des patients âgés souffrant de comorbidités. Chez les patients jeunes, le traitement actuel repose sur le méthotrexate et la cytarabine à haute dose. L'objectif de cette étude était d'évaluer l'efficacité et la faisabilité de ce traitement chez des patients âgés, ainsi que d'évaluer l'impact sur la survie de différents facteurs pronostiques potentiels.

Méthodes. Il s'agit d'une étude rétrospective menée dans deux centres entre janvier 2008 et septembre 2015, incluant 35 patients âgés immunocompétents ayant reçu un traitement de première ligne par méthotrexate haute-dose.

Résultats. Après un suivi médian de 19.8 mois (écart: 1.7 – 73.4 mois), la survie globale médiane était de 39.5 mois (intervalle de confiance à 95% (95% IC): 18.3 – 60.7) et la survie sans progression médiane était de 25.8 mois (95% IC: 5.2 – 46.4). En analyse univariée, l'administration de cytarabine haute-dose et le maintien d'une dose-intensité de méthotrexate > 75% étaient associés à une augmentation de la survie globale ($p = 0.006$ et $p = 0.003$, respectivement) et de la survie sans progression ($p = 0.003$ et $p = 0.04$, respectivement), alors qu'un score MSKCC élevé et la présence de comorbidités sévères, définies par un score CIRS-G ≥ 8, étaient associés à une diminution de la survie globale ($p = 0.02$ et $p = 0.03$, respectivement). Un score CIRS-G ≥ 8 était également associé à une diminution de la survie sans progression ($p = 0.04$).

Conclusions. Les comorbidités et la dose-intensité relative de méthotrexate sont des facteurs pronostiques important chez les patients âgés traités en première ligne pour un lymphome cérébral primitif. Ces résultats doivent être confirmés par des études prospectives.

Mots-clés : Lymphome cérébral primitif ; patients âgés ; méthotrexate haute-dose ; dose-intensité relative ; comorbidités.

Impact of front line relative dose intensity for methotrexate and comorbidities in immunocompetent elderly patients with primary central nervous system lymphoma

ABSTRACT

Background. Primary central nervous system lymphomas (PCNSL) are non-Hodgkin lymphomas strictly localized to the CNS, with specific biology, and which mainly occur in elderly patients with comorbidities. Current treatment in younger patients relies on high-dose methotexate and high-dose cytarabine. The aim of this study was to evaluate the efficacy and feasibility of this treatment in elderly patients and to assess potential prognostic factors associated with survival.

Methods. We conducted a retrospective study in two centers between January 2008 and September 2015 including 35 elderly immunocompetent patients who received first-line treatment with high-dose methotrexate.

Results. With a median follow-up of 19.8 months (range: 1.7 – 73.4 months), median overall survival (OS) was 39.5 months (95% confidence interval (95% CI): 18.3 – 60.7) and median progression-free survival (PFS) was 25.8 months (95% CI: 5.2 – 46.4). In univariate analysis, administration of high-dose cytarabine and achieving a relative dose intensity for methotrexate > 75% were associated with increased OS ($p = 0.006$ and $p = 0.003$, respectively) and PFS ($p = 0.003$ and $p = 0.04$, respectively) whereas a high MSKCC, a PCNSL-specific prognostic score, and comorbidities defined by a CIRS-G score ≥ 8, were associated with decreased OS ($p = 0.02$ and $p = 0.03$, respectively). A CIRS-G score ≥ 8 was also associated with decreased PFS ($p = 0.04$).

Conclusions. Comorbidities and relative dose intensity for methotrexate are important for the prognostic of elderly patients with PCNSL. These results must be confirmed in prospective trials.

Keywords : Primary central nervous system lymphoma ; elderly patients ; high-dose methotrexate ; relative dose intensity ; comorbidities.

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