Primary Central Nervous System Lymphoma: Clinical Characteristics, Treatment Options and Therapeutic Outcome in 36 Patients. A Single Center Experience

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ABSTRACT **Background:** Primary central nervous system lymphoma (PCNSL) is a rare aggressive non-Hodgkin's lymphoma. There are limited data on the management of PCNSL outside of clinical trials.

Objectives: To report experience with three main high-dose methotrexate (HDMTX)-based protocols for PCNSL treatment at one medical center.

Methods: We conducted a retrospective review of the medical records of patients diagnosed with PCNSL who were treated at Soroka Medical Center between 2007 and 2019.

Results: The study included 36 patients, median age 64.9 years; 33 patients received a HDMTX backbone induction therapy, 21 (58.3%) received consolidation treatment in addition. In the entire cohort, 25 patients (75.7%) achieved complete remission (CR, CRu-unconfirmed), with mean progression-free survival (PFS) 32 ± 6.9 months and median overall survival (OS) 59.6 ± 12.4 months. More aggressive regiment such as combination of rituximab, HDMTX, cytarabine and thiotepa had better responses 5 (100%) CR, but also a higher incidence of side effects such as neutropenic fever 5 (100%). In subgroup analysis by age (younger vs. older than 60 years), the PFS was 24.2 vs. 9.3 months, and OS was 64.1 vs. 19.4 months, respectively.

Conclusions: A difference in CR and PFS favored a more aggressive protocol, but the toxicity of the multiagent combinations was significantly higher. The prognosis in younger was better than in older patients, with higher rates of CR, PFS, and OS, although not statistically significant. Overall treatment outcomes are encouraging; however, there is a real need for an adaptive approach for older patients and balancing among the effectiveness and side effects.

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KEY WORDS: primary central nervous system lymphoma (PCNSL), prognosis, treatment

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive variant of non-Hodgkin's lymphoma that is limited to the brain, leptomeninges, eyes, and spinal cord without evidence of systemic disease. It represents 4% of intracranial neoplasms and 4–6% of extranodal lymphomas [1]. Incidence increased from 0.1 per 100,000 in the 1970s to 0.4 per 100,000 in the 1980s, correlating with an increase in the diagnosis of patients ≥ 70 years (1973: 0.2 vs. 2013: 2.1). Incidence rates differed between young and older patients (age 20–29 years [0.08] vs. 70–79 years [4.32]). Although the median overall survival of all patients doubled from 12.5 months in the 1970s to 26 months in the 2010s, this survival benefit was limited to patients < 70 years. Survival in the older population has not changed in the last 40 years (6 months in the 1970s vs. 7 months in the 2010s, $P = 0.1$) [2].

The current treatment of PCNSL is administered in two phases: induction and consolidation.

Given the rarity of PCNSL and the paucity of phase 3 randomized clinical trials, there are different approaches to induction and consolidation regimens. While it is generally agreed on that high dose methotrexate is the backbone of therapy, there is controversy surrounding the choice of additional chemotherapeutic agents as well the role of whole-brain radiation therapy (WBRT). The combination of high-dose methotrexate-based chemotherapy with WBRT yielded a 5-year survival of 50–60% [3]. However, the combination of chemoradiation therapy induced delayed neurotoxicity, particularly in patients aged 60 years and older [4].

Several high-dose methotrexate-based induction regimens, in combination with other chemotherapy agents that penetrate the blood-brain barrier (BBB), have been developed. They can achieve high rates of durable complete response in patients with newly diagnosed PCNSL. The role of rituximab in treating PCNSL is uncertain, and a recent systematic review and meta-analysis concluded that there is no evidence for improvement of overall survival and low certainty of evidence that rituximab improves progression-free survival (PFS) [5].

There are almost no comparative trials between different induction combination regimens. They are different in their dose

of high-dose methotrexate, additional chemotherapeutic agents, and consolidation treatment. There is a difference in the response and survival rate, for example 2-year PFS of 77–79% for the rituximab, methotrexate, procarbazine, and vincristine (R-MPV) protocol [6,7]. Median PFS was not reached in MATRix regimen (high-dose methotrexate, cytarabine, thiotepa, and rituximab) [8].

The price of intensive and toxic treatment necessary to achieve the curative goal may be unacceptable for majority of the patients (older age with co-morbidity), leading to a conservative therapeutic approach [9]. Older age is associated with an accumulation of co-morbidities, such as renal insufficiency, that can lead to frequent dose methotrexate reductions [10].

There are limitations to treat the older population since high-dose chemotherapy with autologous transplantation is too toxic for these patients and WBRT has a deleterious effect and it compromises survival because of neurotoxic effects [11,12].

In this study we reported our experience with three main protocols based on high-dose methotrexate regimen for PCNSL treatment that were used during 2007–2019 at our center.

PATIENTS AND METHODS

We performed a retrospective review of the medical records of patients diagnosed with PCNSL, and who were treated at Soroka Medical Center during the period of January 2007 to December 2019. Patients were excluded if they were younger than 18 years of age, positive for human immunodeficiency viruses (HIV), had histology other than diffuse large B cell lymphoma histological subtype, or had a systemic lymphoma. Data were extracted from patient electronic records.

Patients were risk-stratified according to a modified International Extranodal Lymphoma Study Group (IELSG) score (IELSG/4), which included four criteria; age, Eastern Cooperative Oncology Group (ECOG) performance score, elevated serum lactic acid dehydrogenase (LDH) levels, involvement of deep regions of brain (periventricular, basal ganglia, brainstem, and/or cerebellum) [13].

The toxicity profile was graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.3 [14]. The neurotoxicity was measured as grade 1 and higher nervous system disorder.

Treatment response was determined using the criteria set by the International Primary CNS Lymphoma Collaborative Group criteria [15]. The study was approved by the institutional research ethics board.

STATISTICAL ANALYSIS

Student's *t*-test was used for analyzing continuous variables. Fisher's exact test was used to examine the differences between categorical parameters. All statistical tests were two-sided, and statistical significance was set at $P < 0.05$. Overall survival was estimated using the Kaplan–Meier method. Overall survival was calculated from the day of diagnosis to the date of death from any cause and PFS from the date of treatment initiation to date of relapse or death from any cause.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA) and R version 1.4.1717 (R Core Team, Vienna, Austria).

RESULTS

A total of 36 patients were included in this analysis and their baseline characteristics are summarized in Table 1. The median age was 64.9 years (range 38–82 years), and 25 (69.4%) patients had an ECOG performance score of 2 or more [Table 1].

Table 1. Patients and disease characteristics

Category	All patients (n=36)
Male, n (%)	16 (44%)
Age in years	
Mean ± SD	64.9 ± 12.3
≥ 60 years	24 (66.6%)
Range (years),	38–82
Co-morbidity	
Psychiatric disorder	5 (13.9%)
Chronic lung disease	5 (13.9%)
Chronic renal failure	1 (2.8%)
Prior malignancy	6 (16.6%)
Ischemic heart disease	4 (11.1%)
ECOG	
0–1, n (%)	9 (25%)
± 2, n (%)	25 (69.4%)
Mean LDH (U/L) ± SD	422.6 ± 104.7
Multiple lesions n (%)	22 (61.1%)
Deep lesions	17 (42.2%)
IELSG/4 > 2	21 (58.3%)
Symptoms at diagnosis	
Neuropsychiatric symptoms	16 (44.4%)
Focal neurologic deficit	19 (52.8%)
Seizures	9 (25%)
B symptoms	3 (8.3%)
Ophthalmic workup completed	8 (22.2%)
Ocular involvement	1 (2.8%)
CSF workup completed	25 (69.4%)
Positive cytology or flow	5 (13.8%)

ECOG = Eastern Cooperative Oncology Group, CSF = cerebrospinal fluid, IELSG = International Extranodal Lymphoma Study Group, LDH = lactate dehydrogenase, SD = standard deviation

The disease characteristics are summarized in Table 1. The most common symptom at diagnosis was focal neurologic deficit 19 (52.8%). Seventeen patients (42.2%) had deep lesions on their imaging modality. Twenty-one patients (58.3%) had a high IESLG/4 score > 2. The most common diagnostic imaging was magnetic resonance imaging (MRI). Overall, only 8 patients (22%) had ophthalmic evaluation and 25 (69.4%) had a lumbar puncture with cerebrospinal fluid (CSF) evaluation, more than 50% of the tests were obtained after at least first cycle.

Of 36 patients, 33 received methotrexate backbone therapy; 14 (38.8%) received DeAngelis protocol, 14 (38.8%) R-MPV protocol, and 5 (13.8%) MATRix protocol. One patient received only WBRT. Four patients (11.1%) received fewer than two cycles of methotrexate (3 after starting the DeAngelis protocol, and 1 after MATRix protocol).

Cranial radiation as a consolidation treatment was administered to 10 (71.4%) patients in the DeAngelis protocol, 3 (21.4%) in the R-MPV protocol, and 1 (20%) in MATRix protocol. Five patients (13.8%) proceeded to autologous stem cell transplantation as consolidation, four in the MATRix group, and 1 in R-MPV group. The autograft conditioning regimen was IV carmustine 400 mg/m^2 on day 6, and IV thiotepa 5 mg/kg twice a day on days 5 and 4. Three patients proceeded to ibrutinib maintenance in the R-MPV group. The main characteristics of first line treatments are reported in Table 2.

Table 2. First line treatment data

Palliative care	2 (0.05%)
WBRT alone	1 (0.02%)
High-dose methotrexate-based therapy	33 (91.6%)
Characteristics of high-dose methotrexate-based therapy	
Mean dose of methotrexate per cycle mg/m^2	3000 (2000–3500)
Mean total number of cycles	4.6 (1–7)
Chemotherapy protocol	
DeAngelis	14 (38.8%)
R-MPV	14 (38.8%)
MATRix	5 (11.1%)
Rituximab treatment	18 (50%)
Omaya insertion	14 (38.8%)
Consolidation	
HCT-ASCT	5 (13.8%)
WBRT	16 (44.4%)
Ibrutinib maintenance	3 (0.08%)

HCT-ASCT = high-dose chemotherapy followed by autologous stem cell transplantation, WBRT = whole-brain radiation therapy

During treatment, 61.1% of patients presented with fever, 38.9% with neutropenia, 27.8% with neutropenic fever, and 47.8% with neurotoxicity. Regarding patients who developed neurotoxicity, 12 (70%) were at age ≥ 60, and 9 (52%) received irradiation. There was significant difference in the rate of neutropenic fever: 21.4% in DeAngelis, 15.4% in R-MPV and 100% in MATRix ($P = 0.001$) [Table 3]. Twelve patients in the DeAngelis group (85.7%) and two patients in R-MPV group (14.2%) had an ommaya insertion for intrathecal therapy. Two patients presented with infection and one from bleeding from the ommaya.

Eleven patients (30.5%) had a relapse. In seven (63.6%) patients the relapse was isolated to CNS, but four (36.3%) had a systemic relapse. All received a second line of treatment. The treatment decision was according to the characteristic of the relapse (CNS or systemic), previous WBRT treatment, time of progression from the last high-dose methotrexate, and a patient's characteristics (age, ECOG, renal function).

Four patients experienced late relapse (PFS1 > 3 years). All of them achieved a second CR but had a subsequent relapse and presented with neurological deterioration. Four patients (36.3%) died during a second line of therapy. Only one patient remained free of subsequent relapses after his first relapse.

When comparing the groups of treatment, we found the rate of CR/CRu to be 71.4% in DeAngelis, 71.4% in R-MPV, and 100% in MATRix. Using landmark analysis, the median PFS was 28 ± 7.9, 35.6 ± 7 and 23.5 ± 10.2 months (DeAngelis, R-MPV, MATRix, respectively). The OS after 2 years of follow-up was 64.2%, 50%, and 80% (DeAngelis, R-MPV, MATRix, respectively) [Table 3].

In subgroup analysis by age, ECOG performance status ≥ 2 at diagnosis was present in 58.4% vs. 75% in patients < 60 and ≥ 60 years of age, respectively. The score as measured at the end of therapy was ≥ 2 in 50% vs. 70.9%, respectively.

There were no significant differences among the patients younger than 60 years of age and those older than 60 years of age in the laboratory, biopsy, or imaging characteristics. The older age group showed a trend toward more neuropsychiatric symptoms, with 3 (25%) vs. 13 (54.2%), $P = 0.097$, for the younger than 60 and older than 60 age groups, respectively. The younger age group had more patients undergoing an autologous transplant (4 [33.3%] vs. 1 [4.2%], $P = 0.034$, < 60 and > 60 age groups, respectively). There were no significant differences in the CR rates in the age groups. The median PFS was 24.2 months vs. 9.3 months, and the median OS was 64.1 and 19.4 for the younger vs. older age groups, respectively. These differences did not reach statistical significance [Figure 1A, Figure 1B].

DISCUSSION

Our data summarized the real-world experience of a tertiary care center in managing 36 patients between 2007 and 2019

Table 3. Treatment toxicity and response assessment

	All patients (n=36)	DeAngelis (n=14)	R-MPV (n=14)	MATRix (n=5)	*P* value
Neutropenia n (%)	14 (38.9%)	5 (37.5%)	4 (28.5%)	5(100%)	0.013
Fever with neutropenia n (%)	10 (27.8%)	3 (21.4%)	2 (14.2%)	5 (100%)	0.001
Neurotoxicity n (%)	17 (47.2%)	9 (64.3%)	6 (42.8%)	1 (20%)	0.27
Diarrhea/Vomiting n (%)	4 (11%)	1 (7.1%)	1 (7.1%)	2 (40%)	0.239
Response assessment					
CR/CRu	25/35 (75.7%)	10/14 (71.4%)	10/14 (71.4%)	5 (100%)	0.540
PFS from start of treatment (median months)	32 ± 6.9	28 ± 7.9	35.6 ± 7	23.5 ± 10.2	0.273
Overall survival (median)	59.6 ± 12.4 months				
Overall survival 2 years	20 (60.6%)	9 (64.2%)	7 (50.0%)	4 (80%)	0.516

CR = complete remission, CRu = complete remission-unconfirmed, PFS = progression free survival, R-MPV = rituximab, methotrexate, procarbazine, and vincristine

DeAngelis protocol
- Methotrexate intravenous (IV) 2.5 g/m^2 on weeks 1, 3, 5, 7, and 9
- Vincristine IV 1.4 mg/m^2 on weeks 1, 3, 5, 7, and 9
- Procarbazine per oral 100 mg/m^2 /day for 7 days on weeks 1, 5, 9
- Intrathecal methotrexate 12 mg on weeks 2, 4, 6, 8, and 10
- Leucovorin per oral 20 mg every 6 hours for 12 doses on weeks 1, 3, 5, 7, and 9 following methotrexate
- Dexamethasone per oral tapering dose for 7 days (16, 12, 8, 6, 4, 2 mg on weeks 1–6)
- WBRT was planned for a total dose of 45 Gy in 1.80 Gy fractions (weeks 11–15)
- Cytarabine 3 g/m^2 /day for 2 days on weeks 16 and 19 [16].

R-MPV
- Day 1: Rituximab 500 mg/m^2
- Day 2: methotrexate 3.5 g/m^2 (over 2 hours), vincristine 1.4 mg/m^2
- Days 1 through 7: Procarbazine 100 mg/m^2/day (odd cycles, totally 5–7 cycles), consolidation with high dose cytarabine, with radiation 23.4 Gy or 45 Gy, or high-dose chemotherapy with autologous stem-cell transplant [7,8]

MATRix
- Methotrexate 3·5 g/m^2 on day 1
- Cytarabine 2 g/m^2 twice daily on days 2 and 3
- Rituximab 375 mg/m^2 on day 5 and 0
- Thiotepa 30 mg/ m^2 on day 4
- Consolidation with auto SCT or radiation 36 Gy [9].

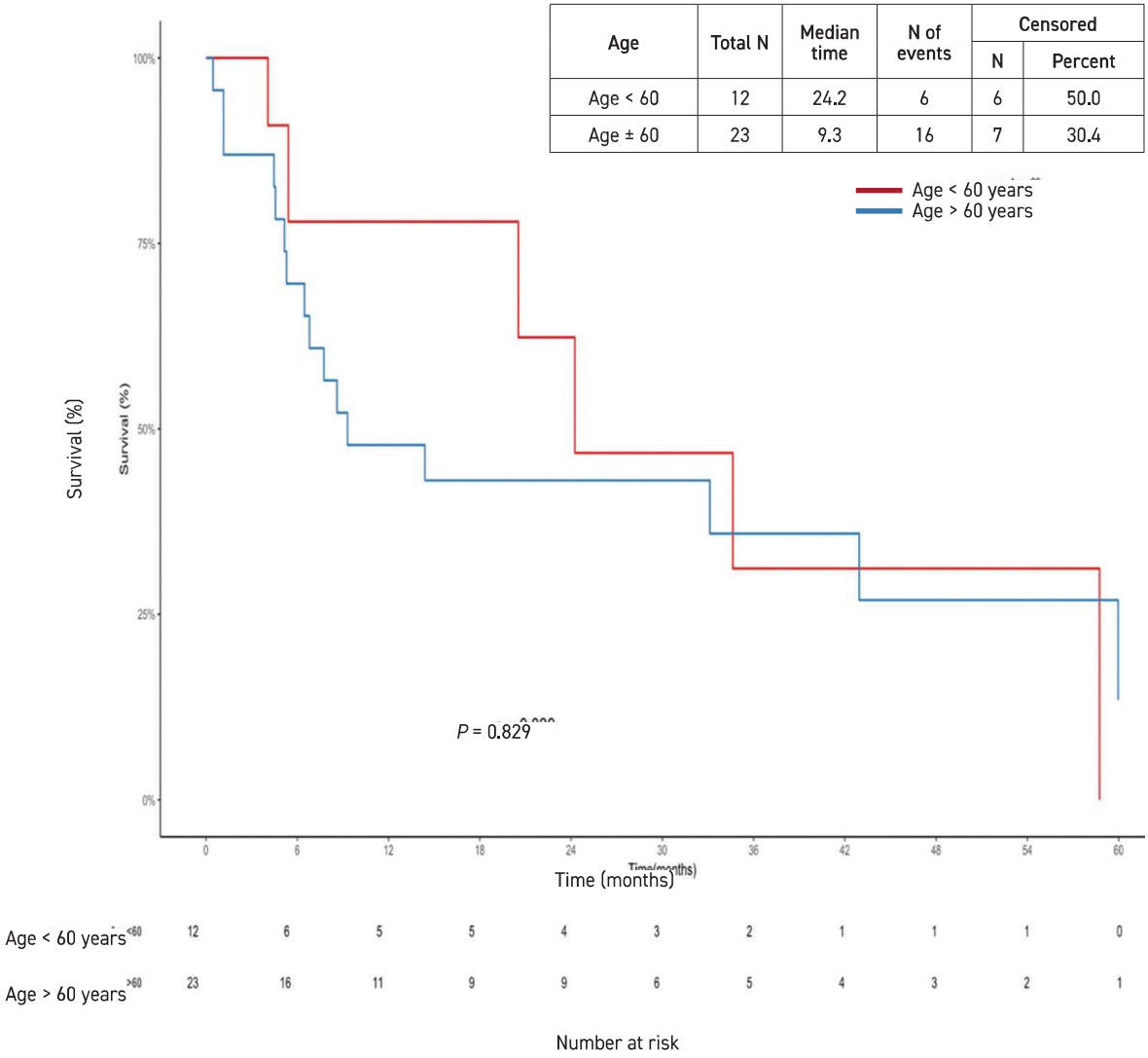
with primary CNS lymphoma outside the setting of a clinical trial. Our population characteristics, including age at presentation and ECOG performance status, were comparable to previously published experiences [17,18].

In our study, the CR/CRu was 75.5%. Median PFS and OS in the entire cohort was 32 and 59.6 months, respectively. These results are significantly better than those found in other studies, which showed CR ranges between 39–50%, median PFS ranges between 9.6–10.5 months, and median overall survival 25.3–29.8 months [16,17]. Although our cohort was small and could not adequately represent the general population, the better outcomes can be explained by the fact that most of our patients received some therapeutic regimen and only 2% received palliative care. Furthermore, most of our patients received a high-dose methotrexate treatment, usually more than 2 grams/m^2, for more than 1 cycle, and usually combined with other chemotherapy. It is well known that combinations of high-dose methotrexate with other chemotherapy significantly improve PFS, as was shown in the meta-analysis and a systematic review of studies about first-line therapy in immunocompetent patients ≥ 60 years with PCNSL until 2014 [19].

Our results reflect the aggressive approach that our center is accustomed to using, which includes a combination of chemotherapy for the disease despite age and performance status. Despite the encouraging results in the total population, the prognosis of older patients in our study remains poor. Older age has consistently been identified as a prognostic factor for overall survival [20]. Older patients are usually offered less aggressive and maybe

Figure 1. Progression-free survival and overall survival by age

[A] Progression-free survival by age; Kaplan-Meir

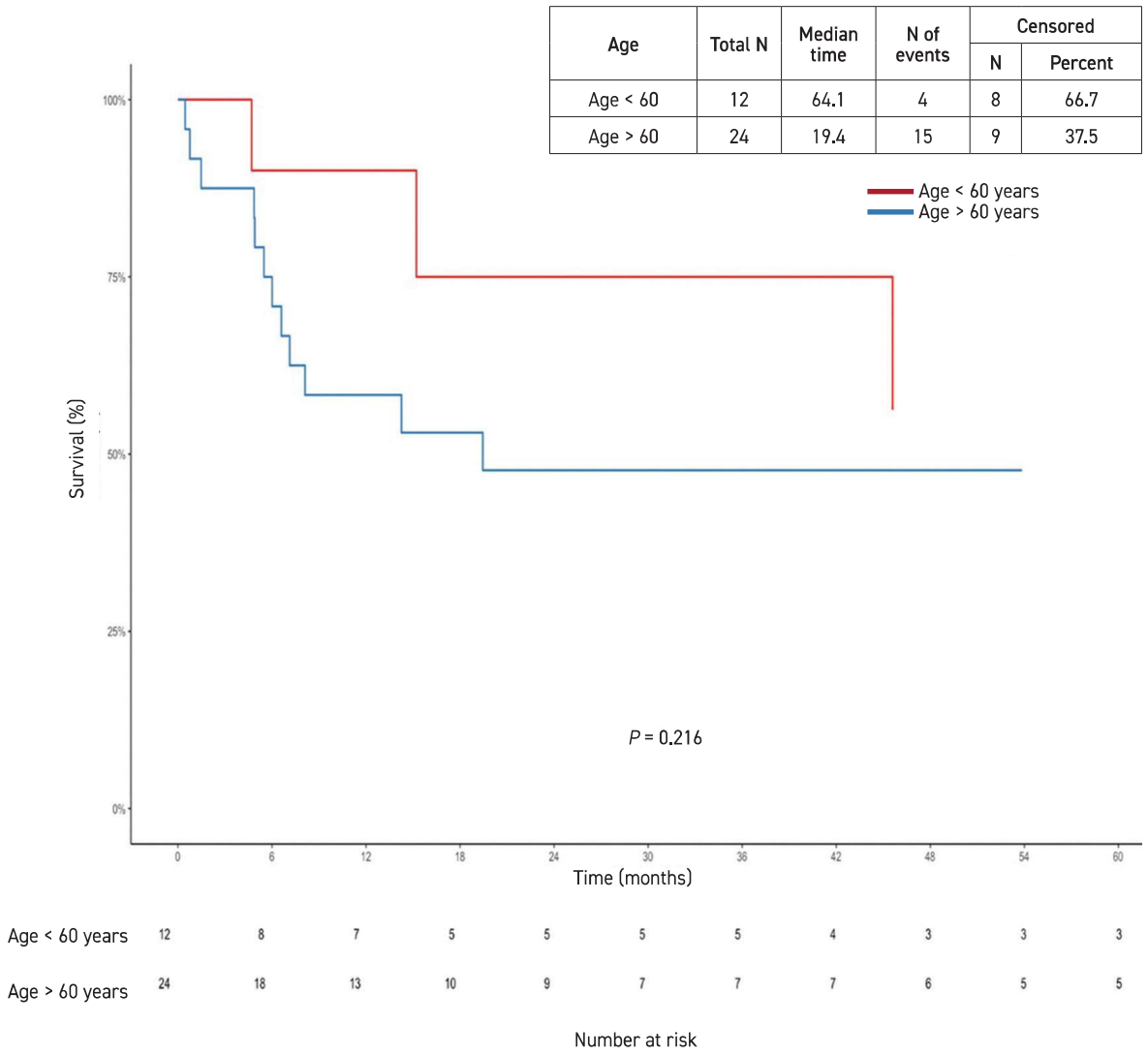


less effective treatment modalities. Approximately 50% of our older patients received a consolidation with irradiation or ibrutinib maintenance. These data can explain their poor outcome since less aggressive treatment secondary to age and frailty status may be partly responsible for a worse outcome. A high rate of neurotoxicity (47.2%) was found in our total population and more prominent in older population ≥ 60 and after radiation. Older patients appeared to have an increased risk for delayed neurotoxicity and declined neurocognitive function after WBRT [21], but the price of neurotoxicity is also high in young populations. Attention, executive function, and verbal memory were significantly impaired in the group that received WBRT consolidation [22].

New combinations of therapies were added to high-dose methotrexate such as rituximab, thiotepa, or consolidation with autologous transplantation. This investigation is highlighted by the persistent standard of care in newly diagnosed patients receiving high-dose methotrexate-based regimens. Over the 12-year period of this study, three main upfront high-dose methotrexate regimens were used in 36 patients (DeAngelis, R-MPV, MATRix).

In our retrospective study we demonstrated a difference in CR and PFS favoring a more aggressive protocol, such as MATRix (CR 100%), but the difference was not significant. In addition, the toxicity of the multiagent combinations, such as MATRix protocol, was significantly higher, with 100% of pa-

[B] Overall survival by age; Kaplan-Meir



tient developing neutropenic fever (compared to 21.4% in De Angelis and 15.4% in R-MPV). Furthermore, a direct comparison between the different protocols was limited due to the small number of patients in our cohort, different follow-up times after treatment, and different supportive care that has improved during the years.

Our study's retrospective design along with the small sample size does not allow for statistically significant conclusions to be drawn regarding treatments and outcomes.

CONCLUSIONS

The presented data suggest that the overall treatment outcomes in practice are encouraging; however, there is a need for an adaptive approach for the older population to balance among the effectiveness and side effects. A prospective and collaborative study is needed to collect more accurate data related to the current therapeutic approach of this rare disease.

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Most people are mirrors, reflecting the moods and emotions of the times;
few are windows, bringing light to bear on the dark corners where troubles fester.
The whole purpose of education is to turn mirrors into windows.

Sydney J. Harris (1917–1986), American journalist for the Chicago Daily News and, later, the Chicago Sun-Times

A writer is, after all, only half his book. The other half is the reader and from the reader the writer learns.

P.L. (Pamela Lyndon) Travers (1899–1996), author, creator of the "Mary Poppins" series

Capsule

Livers beware T and B cells!

Diets high in fat and sugar are known to contribute to chronic inflammation in the liver and subsequent autoimmune reactions, yet the immune responses behind this phenomenon are not well characterized. Studying mice given a high-fat, high-glucose diet, **Clement** and co-authors identified PDIA3, a protein involved in immunogenic cell death, as a peptide presented by cell surface proteins that led to pathogenic T and B cell responses. PDIA3-specific T cells and PDIA3-specific antibodies were sufficient to induce liver toxicity in mice. Anti-PDIA3 was also detected at high levels in the serum of patients with chronic inflammatory liver conditions, suggesting that this mechanism may also be operative in humans.

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