Methotrexate, cytarabine, thiotepa and rituximab (MATRix) chemoimmunotherapy for primary central nervous system lymphoma: a Toronto experience

The MATRix (methotrexate, cytarabine, thiotepa, rituximab) regimen has significantly improved outcomes of patients with primary central nervous system lymphoma (PCNSL). The original trial population, however, was young and fit with few comorbidities. We show that, in a real-world setting, the majority of patients treated with MATRix experienced hematologic toxicity, and 65% of patients developed grade 3 or 4 infectious complications. Dose reductions were made in 68% of patients and dose delays occurred in 49% of patients. Survival was comparable to what has been reported in the literature, but the rate of toxicity was higher than previously described.

The randomized International Extranodal Lymphoma Study Group trial IELSG32 examined outcomes of MATRix followed by consolidation therapy with either autologous stem cell transplant (ASCT) or whole brain radiation in patients with PCNSL.[1] The addition of thiotepa to MATRix had prolonged both overall survival (OS) and progression-free survival (PFS), producing sustained improved outcomes with a 7-year PFS of 50% and an OS of 70%.[2] The IELSG32 trial population was a young and fit population, with a median age of 57 years and the majority of patients (67%) had Eastern Cooperative Oncology Group (ECOG) performance status 0-1. One retrospective multicenter analysis documented poorer outcomes in a population with poorer performance status.[3] We therefore set out to examine the use of MATRix as an induction regimen in a real-world clinical setting in Toronto, Canada.

We performed a retrospective review of patients with a diagnosis of B-cell PCNSL treated at Sunnybrook Health Sciences Centre, Princess Margaret Cancer Centre and St. Michael's Hospital from October 2017 to March 2020. Exclusion criteria included positive serology for human immunodeficiency virus, or systemic lymphoma. A review of electronic health records was performed to retrieve the patients' baseline characteristics, medical history, and treatment details including dose intensity, timing, and response to therapy. For patients deemed eligible for ASCT, induction with MATRix was given at any of the three hospitals, but ASCT was only performed at one center. As such, patients were often seen for transplant later in their treatment course. The local practice evolved to omit thiotepa from the third cycle to allow for improved stem cell collection off the third or fourth cycle. All other dose adjustments were made at the treating physician's discretion.

The primary outcome was assessment of adverse events related to treatment. Secondary outcomes included OS and PFS at 2 years, and response to treatment. Response was assessed by magnetic resonance imaging or computed tomography of the brain using published criteria.[4] Descriptive statistics were used to summarize patients' demographics, treatments and outcomes. The Kaplan-Meier estimator was used to determine the cumulative incidence of OS and PFS at 2 years. Cox regression models were used to investigate the impact of baseline characteristics on outcomes.

A total of 37 patients with a diagnosis of diffuse large B-cell PCNSL were included in this study. The median age of the patients was 58 years (range, 30-69 years). Patients were followed for an average of 16.9 months (range, 3-48 months). The majority of patients received MATRix as first-line therapy (89%). A high number of patients had an ECOG performance status of 2 or more (41%) and 18 patients (49%) had a Charlson Comorbidity Index score of 2 or more. Twenty-four patients (65%) received *Pneumocystis jiroveci* pneumonia prophylaxis throughout treatment with sulfamethoxazole-trimethoprim or atovaquone. Granulocyte colony-stimulating factor was used in all patients for primary prophylaxis.

Dose reductions of any degree were performed in 25 (68%) of the 37 patients during any cycle of MATRix, as shown in Table 1. Treatment was delayed in 18 patients (49%), most often because of infectious complications. Thirty patients (81%) completed all four cycles of MATRix, and 22 patients went on to ASCT. Two (29%) of the seven patients not completing all cycles died before all cycles could be delivered, and the remaining five patients did not complete all four cycles because of toxicity or disease progression while on treatment.

The majority of patients experienced grade 3 or 4 hematologic toxicity during the first cycle of treatment (24.3% grade 3 or 4 anemia, 73.0% grade 3 or 4 thrombocytopenia, 70.3% grade 3 or 4 neutropenia), which often persisted through each cycle of MATRix. Table 2 lists the non-hematologic toxicities experienced by patients. Notably, 24 patients (65%) developed infections on treatment, for a total of 33 individual infectious episodes. Eleven of these episodes were from bacteremia, three from viral infections requiring admission, and twelve were other infections including cellulitis, urinary tract infections, or pneumonia requiring treatment. Seven patients developed severe opportunistic infections, including blastomycosis pneumonia, herpes simplex virus encephalitis, disseminated varicella

Table 1. Doses delivered of the components of the MATRix protocol.

	Number of patients			
	100% dose	75% dose	50% dose or less	Omission
Cycle 1 (37 patients)				
Methotrexate	33	0	0	4
Cytarabine	30	3	2	2
Thiotepa	31	1	0	5
Rituximab	34	0	0	3
Cycle 2 (36 patients)				
Methotrexate	31	2	1	2
Cytarabine	30	5	1	0
Thiotepa	30	2	1	3
Rituximab	36	0	0	0
Cycle 3 (33 patients)				
Methotrexate	28	3	1	1
Cytarabine	25	5	2	1
Thiotepa	7	2	2	22*
Rituximab	32	0	0	1
Cycle 4 (30 patients)				
Methotrexate	27	2	1	0
Cytarabine	22	1	6	1
Thiotepa	23	0	1	6
Rituximab	29	0	0	1

*Routine omission prior to peripheral blood stem cell collection based on local institutional protocols.

zoster virus, *Pneumocystis jiroveci* pneumonia (2 patients), cytomegalovirus pneumonia and pulmonary aspergillosis. Both episodes of *Pneumocystis jiroveci* pneumonia occurred in patients who were not on prophylaxis, and one occurred in a patient receiving MATRix as second-line therapy. Seven patients (19%) developed episodes of febrile neutropenia without any organism being identified. Eight patients (22%) required admission to an intensive care unit during treatment, with a mean duration of stay of 7.5 days. Six patients (16%) developed a venous thromboembolic event including a catheter-associated thrombosis after the third cycle. Two patients developed deep vein thrombosis during the first cycle of treatment, with one episode occurring in a patient receiving MATRix as third-line therapy.

Thirty-five patients (95%) were alive at the end of treatment, and 30 patients had magnetic resonance imaging scans available for analysis. A complete response was seen in seven patients (23%) and a partial response in 18 patients (60%). One patient had stable disease and four patients had progressive disease. Of the 25 patients who responded to treatment, 21 went on to have consolidation therapy with ASCT with thiotepa and carmustine conditioning, and four had consolidation with whole brain radiation. Consolidation was not administered to ten patients because of disease progression, worsening performance status or ineligibility as determined by the treating physician.

The 2-year OS for all patients was 74%, and the median OS was not reached (Figure 1). The 2-year OS was 100% for patients who received ASCT and 49% for patients who did not (P<0.01). The 2-year PFS was 54% and the median PFS was not reached. The 2-year PFS was 78% for patients who received ASCT and 21% for patients who did not (P<0.01). The median PFS was not reached for the 21 patients who received ASCT, and was 10 months (95% confidence interval: 2.2-17.9 months) for patients who did not. Cox regression analyses found that patients with an ECOG performance status greater than 1 showed a trend toward increased mortality, although this was not statistically significant (odds ratio=5.08, 95% confidence interval: 0.80-32.37). MATRix delivered as second- or third-line therapy was not associated with decreased OS (P=0.99). Six patients (16.2%) died during the study period, four from progression of their PCNSL, and two from infectious complications of treatment.

Table 2. Non-hematologic toxicities experienced during the delivery of MATRix.

	Frequency (37 patients)	Percentage
Infection	24	64.9
Febrile neutropenia (no organism identified)	7	18.9
Venous thromboembolism	6	16.2
ICU admission	8	21.6
Acute kidney injury	9	24.3
Gastrointestinal injury/upset	7	18.9
Transaminitis	12	32.4
Mucositis	8	21.6
Neurotoxicity	10	27.0

ICU: Intensive Care Unit.

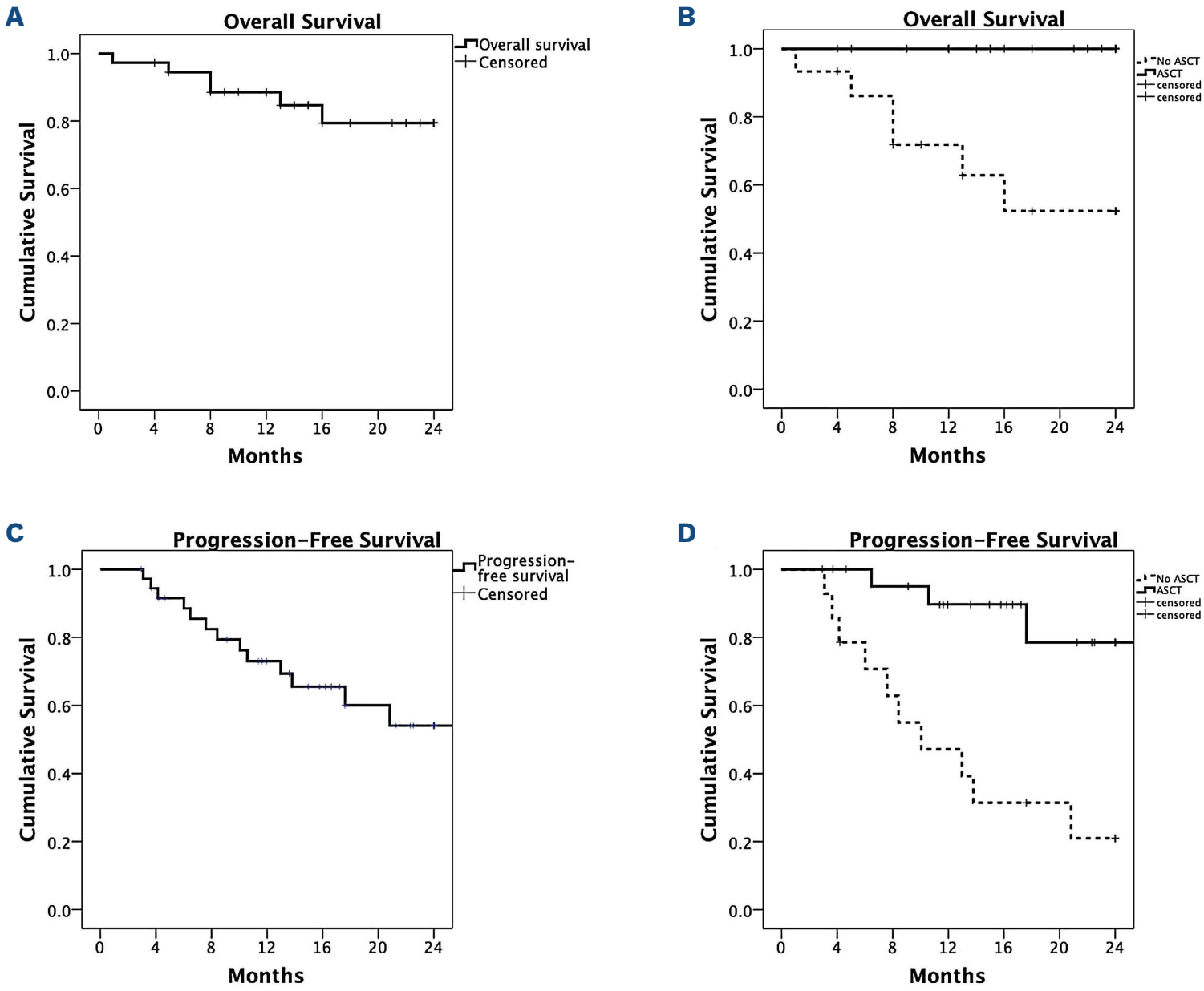

Figure 1. Survival outcomes of patients who received MATRix chemotherapy for the treatment of primary central nervous system lymphoma. (A) Two-year overall survival (74%) for all patients. (B) Two-year overall survival for patients who underwent autologous stem-cell transplantation (100%) and for patients who did not (49%) (P<0.01). (C) Two-year progression-free survival (54%) for all patients. (D). Two-year progression-free survival for patients who underwent autologous stem-cell transplantation (78%) and for patients who did not (21%) (P<0.01). ASCT: autologous stem-cell transplantation.

The rate of toxicity in our study was much higher than that in the IELSG32 study. Only 23% of patients in the original trial developed infections, whereas in our non-selected, real-world population, the infection rate was 65%. Although only two patients died directly from an infectious complication, four out of 25 patients with severe infectious complications were excluded from consolidation therapy because of their severe deconditioning. The infectious complications were more severe than those previously described[3] and included invasive opportunistic infections such as blastomycosis and aspergillosis. In addition, 22% of patients in our cohort required admission to an intensive care unit, for a mean of 7.5 days at some point during treatment; this is a higher percentage than previously reported.[1,3] This high likelihood of admission to an intensive care unit raises questions about the tolerability of MATRix, particularly in patients who are less fit.

There were a significant number of prophylactic or reactive dose reductions, and yet the rate of infections was still high. Although fewer patients achieved a complete response, efficacy was not impacted compared to the IELSG32 trial in this early analysis. High efficacy despite dose reductions was also seen in the study by Schorb *et al.*, in which dose reductions during the first cycle also did not have an impact on PFS or OS.[3] Dose reductions in the IELSG32 trial were not reported. Further studies exploring alternative dosing that could maintain efficacy with less toxicity would be of value. In their real-world experience, Schorb *et al.* found that 2-year OS and PFS were significantly affected by both age and ECOG performance status.[3] The demographics of the populations in our study and that by Schorb *et al.* were similar with a median age of 58 years and 62 years, respectively, and a performance status of >2 in 40% of patients in our study *versus* 51% in that by Schorb *et al.*[3] OS was not significantly affected in either trial, but newer second-line treatments such as ibrutinib and lenalidomide may enhance survival compared to that in the original IELSG32 trial.[5-7]

In conclusion, this is one of the first studies to look at the use of MATRix in a real-world setting with a varied pa-

tient population. There were no restrictions to inclusion based on performance status or age, allowing for a diverse cohort. We highlight infectious complications with a focus on opportunistic infections. Efficacy was maintained even with a significant number of dose reductions. Reducing infections by carefully selecting patients and providing prophylaxis against infections should be considered.

Authors

Adam Suleman,[1] Jiajia Liu,[1] Lisa K. Hicks,[1,2] Adi Klil Drori,[3°] Michael Crump,[1,4] Robert Kridel,[1,4] Anca Prica[1,4#] and Neil Berinstein[1,5#]

[1]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Division of Medical Oncology and Hematology, St. Michael's Hospital, Toronto, Ontario, Canada; [3]AbbVie, Inc., North Chicago, IL, USA; [4]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada and [5]Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, Ontario, Canada

#AP and NB contributed equally as co-senior authors.
°AbbVie had no role in this study and solely reflects this author's current affiliation.

Correspondence:
A. SULEMAN - asule095@uottawa.ca

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Disclosures

No conflicts of interest to disclose. AKD is currently affiliated with AbbVie, but this company had no role in the study.

Contributions

AS and AKD collected data for the manuscript. JL, AP and NB conceptualized the manuscript. AS, JL, LKH, AKD, MC, RK, AP and NB all contributed to writing the manuscript.

Data-sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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