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RESEARCH ARTICLE

Sequential high-dose methotrexate and cytarabine administration improves outcomes in real-world patients with primary central nervous system lymphoma: A report from the Australasian Lymphoma Alliance

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Abstract

Background: Despite recent advances, optimal therapeutic approaches applicable to subpopulations with primary central nervous system (CNS) lymphoma outside of clinical trials remain to be determined.

Methods: We performed a retrospective study of immunocompetent, adult patients with histologically confirmed diffuse large B-cell lymphoma of the CNS (PCNSL). 190/204 (93%) patients (median age: 65) received one of five high-dose methotrexate (HD-MTX) containing chemotherapy regimens: MPV/Ara-C (HD-MTX, procarbazine, and vincristine, followed by cytarabine [Ara-C]) (n = 94, 50%), MATRix (HD-MTX, Ara-C, thiotepa, and rituximab) (n = 19, 10%), HD-MTX/Ara-C (n = 31, 16%), HD-MTX monotherapy (n = 35, 18%) and MBVP (HD-MTX, carmustine, teniposide, prednisolone) (n = 11, 6%).

Results: Cumulative median HD-MTX and Ara-C doses were 17 g/m^2 (range: 1–64 g/m^2) and 12 g/m^2 (0–32 g/m^2) respectively. Using 14 g/m^2 as the reference dose, the median HD-MTX relative dose intensity (HD-MTX-RDI) was 1.25 (0.27-4.57) with 84% receiving > 0.75. The overall response rate (ORR) was 72% (complete response: 50%) after completing HD-MTX. At a median follow-up of 3.41 years (0.06–9.42), progression-free survival (PFS) and overall survival (OS) were different between

chemotherapy cohorts, with the best outcomes achieved in the MPV/Ara-C cohort (2-year PFS 74%, 2-year OS 82%; $p = 0.0001$ and $p = 0.0024$ respectively). On multivariate analysis, MPV/Ara-C administration and HD-MTX-RDI > 0.75 were associated with longer PFS and OS.

Conclusion: Sequential, response-adapted approaches can improve outcomes, even in older patients who are ineligible for a high-intensity concurrent chemotherapy approach and do not undergo traditional consolidative strategies.

KEYWORDS
cytarabine, DLBCL, high-dose therapy, methotrexate, PCNSL, retrospective studies

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) of the central nervous system (CNS) (henceforth referred to as PCNSL) arises within the brain, spinal cord, leptomeninges, or eyes [1]. PCNSL is a rare, aggressive high-grade B-cell lymphoma, with outcomes substantially inferior to systemic DLBCL (30.1% 5-year overall survival compared with 60%–65%) [1, 2].

Currently, there is no standard of care frontline treatment regimen universally used for patients with this diagnosis. High-dose methotrexate (HD-MTX) has been shown to be tumoricidal in the brain and CSF at ≥1000 and ≥3000 mg/m^2, respectively, and forms the backbone of curative-intent chemotherapy regimens [3]. Adequate HD-MTX, both in terms of cumulative dose and dose intensity, is essential to improving outcomes in patients but this can be challenging in older, frailer patients, particularly those with renal impairment [4–6]. The addition of cytarabine (Ara-C) to HD-MTX has further improved survival outcomes and is routinely incorporated into contemporary regimens, either concurrently within treatment cycles or sequentially [7–11]. MATRix (HD-MTX, Ara-C, thiotepa, and rituximab), containing concurrent HD-MTX and Ara-C, has become a standard of care regimen, after encouraging results observed in the International Extranodal Lymphoma Study Group phase 2 trial (IELSG32) trial (2-year progression-free survival [PFS] 61%, overall survival [OS] 69%) [7, 12]. However, the median age of patients in routine clinical practice is 10 years older than patients enrolled in IELSG32, with only 20% of those ineligible for trial entry deemed suitable for MATRix in the real-world setting and most requiring dose reduction due to toxicity [2, 7, 13]. Comparable outcomes can be achieved, even in older patients, with MPV/Ara-C (HD-MTX, procarbazine, vincristine, and Ara-C) which delivers HD-MTX and Ara-C in a sequential rather than concurrent manner [5, 11]. The anti-CD20 antibody, rituximab, is also routinely incorporated into modern chemoimmunotherapy treatment regimens despite conflicting evidence regarding its benefit [12, 14–16].

Patients responding to induction often undergo consolidative strategies, namely whole brain radiotherapy (WBRT) or autologous stem cell transplantation (ASCT), with the latter recently favoured due to a lower rate of neurotoxicity [12, 17]. Nonetheless, many patients are precluded from ASCT due to age, post-induction chemotherapy toxicity, or co-morbidities.

Optimal therapeutic approaches in subpopulations with PCNSL (i.e., older patients or those with pre-existing co-morbidities including renal impairment) remain to be determined and outcome data in these populations are incomplete. The aim of this Australasian Lymphoma Alliance (ALA) international retrospective study was to describe outcomes from frontline chemotherapy strategies for adult patients with PCNSL in Australia and Singapore in the modern era to inform future research directions.

2 | METHODS

We performed a retrospective study of consecutive, immunocompetent, adult patients (≥ 18 years old) with histologically-confirmed PCNSL as per the World Health Organisation 2017 classification from eleven academic hospital sites (10 Australian, one Singaporean) over a 10-year period (January 1, 2009–December 31, 2018) [1]. Patients with a minimally immunosuppressed state (i.e. low-dose steroids [prednisolone ≤ 10 mg or equivalent] or steroid-sparing agents for inflammatory conditions, HIV-positive patients with undetectable viral loads) were included. Treatment was determined by the treating clinician or by institutional practice.

Data were collected using an electronic case report form from institutional databases. Information collected included baseline patient demographics, DLBCL subtype according to Hans classification as assessed by an institutional pathologist, Eastern Cooperative Oncology Group (ECOG) performance status (PS), prognostic information as per IELSG criteria, time from diagnosis to day one of chemotherapy, chemotherapy administered (including a number of cycles, dosing, dose reduction and use of rituximab), consolidative strategies (i.e., WBRT or ASCT for patients with stable disease or better after chemotherapy), neurotoxicity and other major adverse events [18–20]. Neurotoxicity was assessed retrospectively from clinical records and graded as per Radiation Therapy Oncology Group criteria [21]. Renal impairment was defined as 60 mL/min or less (Cockroft-Gault equation or estimated glomerular filtration rate) [22, 23].

Survival analysis was restricted to patients treated with HD-MTX-containing chemotherapy regimens. Analysis was performed on an intention-to-treat basis. The primary endpoint was a 2-year PFS.

Secondary endpoints were: 2-year OS, overall response rate (ORR) after HD-MTX (but prior to any consolidative strategies) assessed by local institutions as per international working group for PCNSL criteria, 2-year PFS and OS by age (≤ 60 years vs. > 60 years), treatment strategy, use of rituximab, consolidative strategy (WBRT or ASCT) and IELSG risk criteria [24]. Median follow-up was calculated for patients alive at the time of census.

Survival endpoints were estimated from the date of diagnosis to the date of disease progression or death, censored at the date of the last patient encounter. PFS and OS were estimated by the Kaplan-Meier log-rank method. The Mann-Whitney U (or paired t-test) and Fisher exact tests were used for continuous and discrete variables, respectively.

Cox regression modeling was performed for univariate (UVA) and multivariate analysis (MVA). For variables with sufficient data (exclusion criteria: ≥20% missing cases), a parsimonious, stepwise multivariable model was constructed, with entry and exit criteria set at $p = 0.05$ and $p = 0.1$, respectively. Cumulative MTX was categorized in quanta of 3.5gm/m^2. Analysis of the impact of HD-MTX was restricted to patients who received more than two cycles to address the confounder of early censoring prior to receiving adequate therapy. As the 'expected dose' was either not pre-defined in patients treated with the response-adapted MPV/Ara-C regimen, or not recorded in patients treated with older HD-MTX regimens, relative HD-MTX dose intensity (HD-MTX-RDI) was calculated by normalising the cumulative MTX dose administered against a reference dose of 14 g/m^2, which equates to MATRix or MTX/Ara-C without dose attenuation [4, 7, 10, 12]. Ara-C dosing was not included in Cox regression modeling as Ara-C administration in the MPV/Ara-C cohort was restricted to patients who achieved an ORR after HD-MTX. Data was analyzed using IBM SPSS Statistics v23 and GraphPad PRISM 10.

The study was undertaken by the ALA. Patient data were anonymised at source and the study was performed according to the principles of the Declaration of Helsinki and institutional ethical guidelines.

3 | RESULTS

3.1 | Patient characteristics

Two-hundred and four of the 227 (90%) patients entered into the database met the criteria for inclusion, 190 (93%) of whom received HD-MTX-containing chemotherapy (Figure 1). Detailed patient and chemotherapy regimen characteristics are summarised in Table 1 (with additional information provided in Table S1).

3.2 | Treatment summary

Five HD-MTX-containing chemotherapy regimens were used during the census period: MPV/Ara-C (HD-MTX, procarbazine, vincristine, followed by Ara-C) ($n = 94$, 50%), MATRix (HD-MTX, Ara-C, thiotepa, and rituximab) ($n = 19$, 10%), HD-MTX/Ara-C (n = 31, 16%), HD-MTX monotherapy ($n = 35$, 18%) and MBVP (HD-MTX, carmustine, teniposide, and prednisolone) ($n = 11$, 6%). The median time to treatment from diagnosis was 11.5 days (1–520 days), with one patient treated 520 days after initial histological diagnosis due to initial refusal of therapy for low-volume disease. Rituximab was administered to 164 (86%) patients, including 100% of those treated with MATRix and 91 (97%) treated with MPV/Ara-C (Table 1). Intrathecal chemotherapy was used in 36 (19%), 28 (78%) of whom received MPV/Ara-C.

3.3 | HD-MTX and HD-Ara-C dosing

HD-MTX dosing data were available for 174 patients (92%). The median number of cycles administered was 5 (range: 1–10), with a median HD-MTX dose of 3.5 g/m^2 (1–8 g/m^2) per cycle, equating to a cumulative median dose of 17 g/m^2 (1–64 g/m^2). A minimum of four cycles of HD-MTX was administered to 161 (85%) patients, including 86 (91%) treated with MPV/Ara-C. Cumulative dosing was highest in the HD-MTX monotherapy and lowest in the MBVP cohorts, respectively, at 28 g/m^2 (3–64 g/m^2) and 11.2 g/m^2 (10.3–12 g/m^2). HD-MTX dose reduction was required in 77 patients (43%, data not available [N/A]: 11 [6%]), with 57 (74%) dose modifications occurring after the first cycle) (Table 2A). Renal impairment ($n = 32$, 18%) and older age ($n = 21$, 12%) were the most common reasons for dose reduction. Dose modifications were most common in the HD-MTX monotherapy cohort ($n = 20$, 61%).

HD-MTX-RDI was calculated for 159 patients (84%) (excluded: missing data $n = 13$ [7%], received two cycles or less: 18 [9%]). The median HD-MTX-RDI was 1.25 (0.27–4.57) with 134 (84%) receiving HD-MTX-RDI > 0.75. The highest HD-MTX-RDI was in the HD-MTX monotherapy cohort at 2.11 (0.5–4.57). Eighty-eight patients (55%) were treated with MPV/Ara-C (median HD-MTX-RDI: 1.25 [0.5–1.75], HD-MTX-RDI > 0.75: 79 [90%]).

Ara-C treatment was planned for 155 patients (82%). Of these, 128 (83%) received Ara-C. The median cumulative Ara-C dose was 12 g/m^2 (0–32 g/m^2) (missing data $n = 4$ [2%]) (Table 1). Dose modifications were required in 54 (42%) patients, most commonly due to advanced age ($n = 16$, 10%) (Table 2B). Twenty-four of the 27 patients (89%) who did not receive Ara-C despite the intention to treat were in the MPV/Ara-C cohort.

3.4 | Treatment outcomes

After completion of HD-MTX, ORR, and complete response (CR) were 72% and 50%, respectively. Responses were highest in MPV/Ara-C (ORR: 85%, CR: 56%) but comparison between cohorts was not possible due to missing data and small numbers.

At a median follow-up of 3.41 years (0.06–9.42), the 2-year PFS and OS were 55% (95% confidence interval [95%CI]: 47–62) and 77% (95%CI: 70–83), respectively (Figure 2A,B). PFS and OS varied between chemotherapy regimens, with the highest PFS and OS

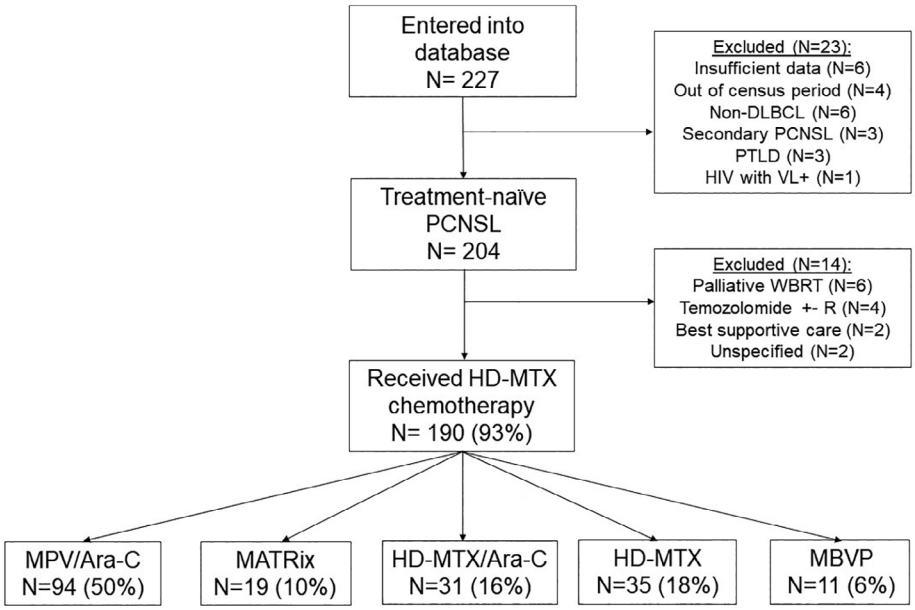

FIGURE 1 Consort diagram. MPV/Ara-C: methotrexate, procarbazine, vincristine, followed by cytarabine. MATRix: methotrexate, cytarabine, thiotepa, rituximab. Methotrexate (HD-MTX)/cytarabine (Ara-C): methotrexate, cytarabine (+/- rituximab). HD-MTX: methotrexate (+/- rituximab). MBVP: methotrexate, carmustine, teniposide, prednisolone (+/- rituximab) [patients enrolled in HOVON105/ALLG NHL4 study] [16]. HIV VL, human immunodeficiency virus viral load; non-DLBCL, non-diffuse large B-cell lymphoma histology; PTLD, post-transplant lymphoproliferative disorder; R, rituximab; WBRT, whole brain radiotherapy. Fourteen patients (7%) did not receive HD-MTX-containing chemotherapy. These patients were older than those who received HD-MTX-containing chemotherapy (72 years [range: 63–85] vs. 67 years [25-87]; $p = 0.001$). Incomplete follow-up data precluded progression-free survival (PFS) and overall survival (OS) estimates in this cohort.

observed in the MPV/Ara-C cohort (2-year PFS 74%, $p = 0.0001$; 2-year OS 82%, $p = 0.0024$) (Figure 2C,D). Patients receiving seven cycles of MPV (due to not achieving CR after five cycles) had longer PFS than those receiving five cycles, but OS did not differ (2-year PFS 94% vs. 68%, hazard ratio [HR] = 0.35, 95%CI = 0.14–0.87, $p = 0.03$; 2-year OS 94% vs. 92%, HR = 0.92, 95%CI = 0.27–3.19, $p = 0.90$) (Figure 2E,F).

In patients over 60 years of age, 2-year PFS was inferior to younger counterparts (48% vs. 69%, HR = 1.88, 95%CI = 1.22–2.89, $p = 0.009$) but there was no difference detected in terms of 2-year OS (75% vs. 79%, HR = 1.41, 95%CI = 0.85–2.36, $p = 0.2$) (Figure 3A,B). Rituximab use was associated with improved 2-year PFS but not OS (58% vs. 38%, HR = 0.54, 95%CI = 0.28–1.05, $p = 0.02$; 78% vs. 61%, HR = 0.68, 95%CI = 0.34–1.35, $p = 0.19$) (Figure S1).

At the end of census period, 128 patients (67%) were alive. The most common cause of death was disease progression ($n = 55$, 29%). Treatment-related mortality (TRM) was 4%.

3.5 | Consolidative therapies

Fifty-eight patients (31%) received post-induction chemotherapy WBRT (20–45 Gy). These patients were younger than those who did not receive WBRT (median age: 58 years vs. 68 years, $p < 0.0001$). Consolidative WBRT was not associated with improvement in either PFS or OS when compared to patients receiving no consolidation (neither WBRT nor ASCT) but the analysis was underpowered (PFS: HR = 0.70, 95%CI = 0.39–1.23, $p = 0.24$; OS: HR = 0.82, 95%CI = 0.42–1.63, $p = 0.58$) (Figure 3C,D). Another nine patients (5%) received WBRT for relapsed/refractory disease.

Fifteen patients (8%) proceeded to ASCT after induction chemotherapy, including 7/19 (37%) treated with MATRix. Prior to ASCT, 10 (67%) were in CR and four (27%) in partial response (PR, data N/A: $n = 1$). Two patients received both ASCT and WBRT and three patients received ASCT for relapsed disease. Patients receiving ASCT were younger than those who did not receive consolidation (median age: 55 years vs. 67 years, $p = 0.0003$). Survival analysis was not performed due to low numbers in the ASCT cohort.

3.6 | Neurotoxicity

Neurotoxicity data were available for 109 patients (57%). Neurotoxicity was documented in 46 patients (24% of the total cohort, 42% of patients with available data), of whom 29 (63%) received WBRT (23 after induction chemotherapy, six at relapse) and four (9%) underwent ASCT; two patients received both. The median age of patients with neurotoxicity was 64 years (25–87). Neurocognitive dysfunction was more common in patients who received WBRT (29/47 [61%] versus 17/62 [27%], $p = 0.0004$).

3.7 | Cox regression models for PFS and OS

On UVA, four covariates were associated with longer PFS: age 60 or less, rituximab administration, MPV/Ara-C chemotherapy use, and

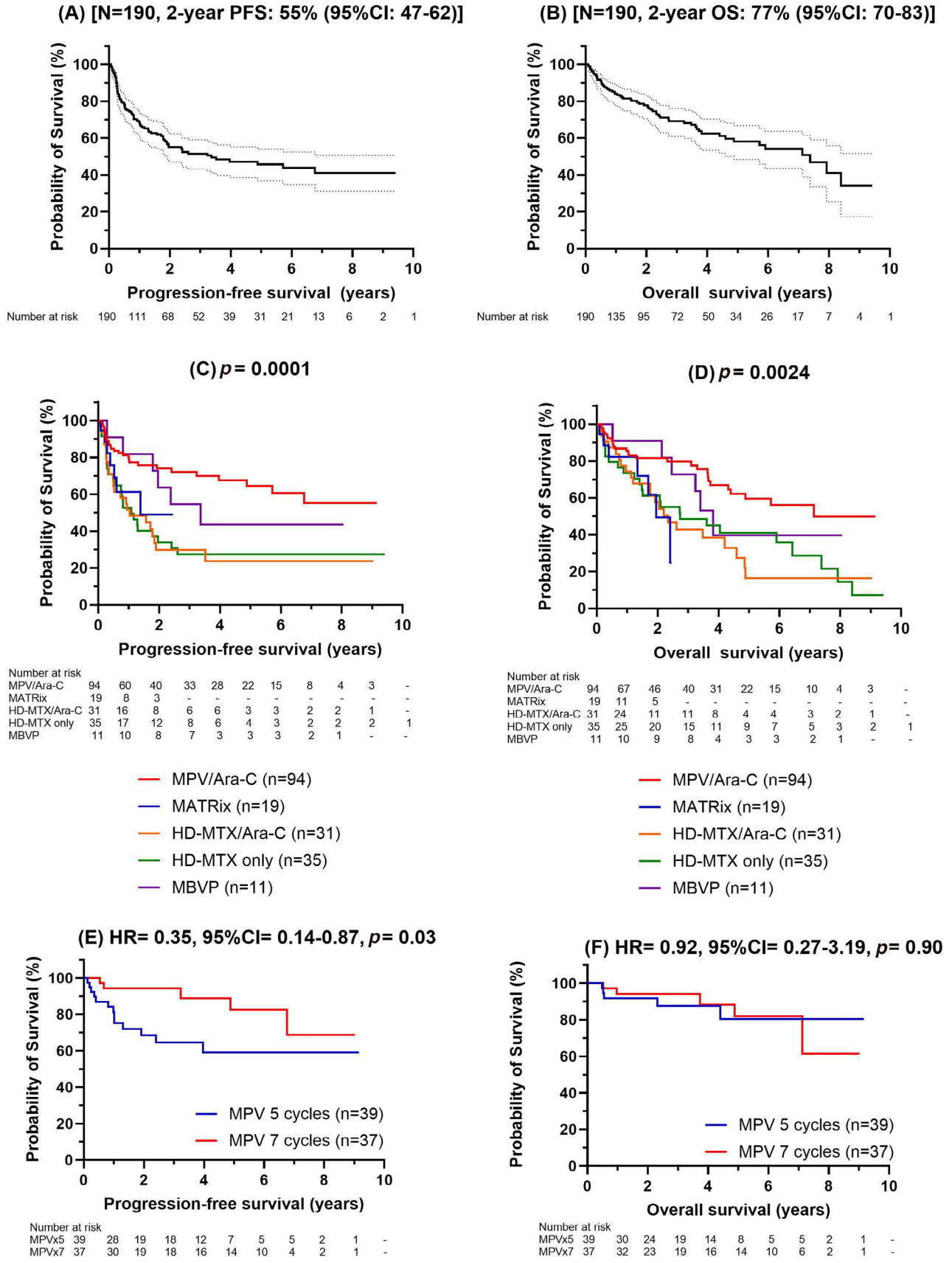

FIGURE 2 Survival graphs. Median follow-up: 3.41 years (0.06–9.42). (A) Progression-free survival and (B) Overall Survival of high-dose methotrexate (HD-MTX) cohort [all regimens]. (C) Progression-free survival and (D) Overall survival by chemotherapy cohort. (E) Progression-free survival and (F) Overall survival by seven versus five cycles of MPV.

TABLE 1 Patient characteristics. Further details are available in Table S1. Cohorts as per intention-to-treat (NB HD-MTX/Ara-C cohort includes one patient who did not receive cytarabine [Ara-C] while two patients in the HD-MTX monotherapy cohort received Ara-C). International Extranodal Lymphoma Study Group (IELSG) criteria could not be calculated due to incomplete data (i.e. $n = 106$ [56%] of patients had at least one missing variable). CSF was involved (cytology +/- flow cytometry) in 25 (13%) patients, but data was only available for 113/190 (60%) patients. HD-MTX-RDI for MBVP is not shown as data only available for 2/11 (18%). Median follow-up was calculated for surviving patients (i.e. patients alive at the time of census).

	Entire cohort	MPV/Ara-C	MATRix	HD-MTX/Ara-C	HD-MTX	MBVP
Number (%)	190	94 (50%)	19 (10%)	31 (16%)	35 (18%)	11 (6%)
Median age (range)	65 (25-87)	65 (25-86)	63 (27-74)	65 (52-76)	68 (27-87)	59 (38-70)
Male sex, *n* (%)	103 (54%)	54 (57%)	14 (74%)	14 (45%)	17 (49%)	4 (36%)
ECOG 2–4, *n* (%)	54 (28%)	32 (34%)	4 (21%)	8 (26%)	7 (20%)	3 (27%)
Deep structure involvement (%)	116 (61%)	66 (70%)	8 (42%)	17 (55%)	22 (63%)	3 (27%)
Impaired renal function (%)	12 (6%)	9 (10%)	0 (0%)	2 (7%)	1 (3%)	0 (0%)
Median follow-up, years [surviving patients], years (days)	3.41 (0.06–9.42)	3.39 (0.08–9.16)	1.88 (0.06–2.46)	5.21 (0.09–9.04)	6.09 (0.11–9.42)	4.06 (3.35–8.06)
Rituximab administered, *n* (%)	164 (86%)	91 (97%)	19 (100%)	23 (74%)	25 (71%)	6 (55%)
Cumulative HD-MTX g/m^2, median (range)	17 (1–64)	17.5 (2.5–24.5)	13.5 (1–17.5)	14 (17.5–22)	28 (3–64)	11.2 (10.3-12)
HD-MTX-RDI median (range)	1.25 (0.27–4.57)	1.25 (0.5–1.75)	1 (0.61–1.25)	1 (0.27–1.57)	2.11 (0.5–4.57)	N/A
HD-MTX-RDI > 0.75 (% of available data)	134/159 (84%)	79/88 (90%)	12/14 (86%)	17/26 (65%)	25/29 (86%)	N/A
Cumulative Ara-C mg/m^2, median	12 (0–32)	12 (0–12)	32 (4–32)	6 (0–32)	N/A	8 (0–8)
ORR after HD-MTX, *n* (%)	136 (72%)	80 (85%)	12 (63%)	21 (68%)	20 (57%)	3 (27%)
CR, *n* (%)	94 (50%)	53 (56%)	11 (58%)	15 (48%)	14 (40%)	1 (9%)
Post induction WBRT (20–45 Gy), *n* (%)	58 (31%)	28 (30%)	4 (21%)	10 (32%)	10 (29%)	6 (55%)
Post induction ASCT, *n* (%)	15 (8%)	5 (5%)	7 (37%)	2 (6%)	0 (0%)	1 (9%)
Neurotoxicity, *n* (%)	46 (24%)	26 (28%)	7 (37%)	8 (26%)	4 (11%)	1 (9%)
Treatment-related mortality, %	4%	7%	5%	0%	0%	0%

Note: Neurotoxicity missing data $n = 81$ (43%) [see Table S1].

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; HD-MTX, methotrexate (+/- rituximab); HD-MTX-RDI, HD-MTX relative dose intensity; MATRix, methotrexate, cytarabine, thiotepa, rituximab; MBVP, methotrexate, carmustine, teniposide, prednisolone (+/- rituximab); methotrexate (HD-MTX)/cytarabine (Ara-C), methotrexate, cytarabine (+/- rituximab); MPV/Ara-C, methotrexate, procarbazine, vincristine, followed by cytarabine; ORR, overall response rate; WBRT, whole brain radiotherapy.

maintaining HD-MTX-RDI > 0.75 (Table 3A). The latter two covariates were also associated with longer OS. On MVA, age 60 or less, use of MPV/Ara-C and HD-MTX-RDI > 0.75 were associated with longer PFS, with the latter two covariates also associated with prolonged OS (Table 3B).

4 | DISCUSSION

Treatment of patients with PCNSL is an ongoing therapeutic challenge, particularly for those ineligible for clinical trials or consolidative strategies due to age or co-morbidities. We collected data on 204 patients, of which 190 (93%) were deemed suitable for HD-MTX-containing regimens. Despite a median age of 65 (range: 25–87), with two-thirds over the age of 60 and a quarter of patients with a reduced performance status (ECOG PS 2–4) prior to therapy, the 2-year PFS and OS of 55% and 77%, respectively, with a TRM of 4%, are comparable to reported outcomes of the IELSG32 (MATRix) prospective clinical trial (2-year PFS 61%, OS 69%), as well as contemporary retrospective data (estimated 2-year PFS and OS 36%–56% and 50%–64%, respectively; TRM 5%–6.9%) [4, 6, 13, 25].

Adequate delivery of HD-MTX may account for these encouraging results. Two recent large retrospective studies demonstrated the association between maintaining both dose intensity and cumulative dose of HD-MTX, respectively, to improved outcomes [4, 6]. The cumulative MTX dose in our cohort (17 g/m^2 with a median range of 11.2–28 g/m^2 for the different chemotherapy cohorts) was comparable to both of these studies (6.4–20 mg/m^2). Furthermore, utilizing the same reference dose of 14 g/m^2 as used by Martinez-Calle et al., the HD-MTX-RDI in our study was higher than reported in their cohort (median 1.25 versus 0.6 and > 0.75 84% versus 46%, respectively) [4]. Ara-C has also been shown to improve PFS and is routinely incorporated into contemporary regimens [9–12]. While the impact of Ara-C could not be assessed in our study, the median dose administered to

TABLE 2 (A) High-dose methotrexate (HD-MTX) dose modification and (B) Cytarabine (Ara-C) dose modification. HD-MTX dose modification data was recorded for 179 (94%) patients (although actual dosing data available only for n=174 [92%] of patients). HD-MTX dose modification is expressed as a percentage of patients with available data (e.g. $n = 179$ for the total cohort). 'Received but dose modified' Ara-C cohort is expressed as a percentage of those who received Ara-C (e.g. $n = 128$ for the total cohort). Ara-C modification/omission reason expressed as a percentage of the total intended to receive Ara-C treatment.

(A) HD-MTX dose modification						
	Entire CIT cohort ($n = 179$)	**MPV/Ara-C ($n = 94$)**	**MATRix ($n = 18$)**	**HD-MTX/Ara-C ($n = 30$)**	**HD-MTX ($n = 33$)**	**MBVP ($n = 4$)**
Full dose administered	102 (57%)	61 (65%)	9 (50%)	17 (57%)	13 (39%)	2 (50%)
Dose modification	77 (43%)	33 (35%)	9 (50%)	13 (43%)	20 (61%)	2 (50%)
Renal impairment	32 (18%)	13 (14%)	3 (17%)	7 (23%)	7 (21%)	2 (100%)
Cytopenia(s)	6 (3%)	2 (2%)	1 (6%)	1 (3%)	2 (6%)	0 (0%)
Mucositis	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neurotoxicity	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Age	21 (12%)	11 (12%)	1 (6%)	2 (7%)	7 (21%)	0 (0%)
Other	9 (5%)	4 (4%)	4 (22%)	0 (0%)	1 (3%)	0 (0%)
Unknown	7 (4%)	2 (2%)	0 (0%)	3 (10%)	2 (6%)	0 (0%)
Missing data	11 (6%)	0 (0%)	1 (5%)	1 (3%)	2 (6%)	7 (64%)

(B) Ara-C dose modification					
	All ($n = 155$)	**MPV/Ara-C ($n = 94$)**	**MATRix ($n = 19$)**	**HD-MTX/Ara-C ($n = 31$)**	**MBVP ($n = 11$)**
Received Ara-C	128 (83%)	70 (74%)	18 (95%)	30 (97%)	10 (91%)
Omitted Ara-C	27 (17%)	24 (26%)	1 (5%)	1 (3%)	1 (9%)
Received but dose modified	54 (42%)	30 (43%)	8 (44%)	15 (50%)	1 (10%)
Modification/omission reason					
Renal impairment	10 (6%)	6 (6%)	2 (11%)	2 (6%)	0 (0%)
Cytopenia(s)	3 (2%)	2 (2%)	1 (5%)	0 (0%)	0 (0%)
Mucositis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neurotoxicity	2 (1%)	0 (0%)	1 (5%)	1 (3%)	0 (0%)
Age	16 (10%)	9 (10%)	1 (5%)	6 (19%)	0 (0%)
Other	14 (9%)	10 (11%)	3 (16%)	1 (3%)	0 (0%)
Unknown	9 (6%)	3 (3%)	0 (0%)	5 (16%)	1 (9%)
Missing data	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

our cohort is comparable to those of modern regimens and is a likely contributing factor to the survival outcomes in our cohort.

Fifty percent of patients were treated with MPV/Ara-C in our study which is reflective of Australian clinical practices during this census period. MPV/Ara-C uses a response-adapted, sequential rather than concurrent protocol for HD-MTX and Ara-C delivery. Ninety-one percent of patients treated with MPV/Ara-C received at least four cycles of HD-MTX at a median dose of 3.5 g/m^2 per cycle, translating to high HD-MTX-RDI (median 1.25, > 0.75: 90%) and cumulative MTX dose (median 17.5 g/m^2 [2.5–24.5 g/m^2]). Of note, while cumulative HD-MTX dose did not reach statistical significance when assessing the impact on PFS of the entire cohort (HR = 0.9, 95%CI = 0.8–1.1, $p = 0.07$), patients treated with 7 cycles rather than 5 cycles of MPV had improved PFS, suggesting that cumulative HD-MTX dose may still be important in improving outcomes.

Survival outcomes of the MPV/Ara-C cohort are comparable to recent 'real-world' MATRix data [13]. In their multi-center retrospective study of 427 patients, Schorb et al. demonstrated 2-year PFS of 56% and OS of 64% in 156 patients treated with MATRix outside of a clinical trial. However, the median age of those patients was 62, while another 217 patients did not receive MATRix and thus were excluded from the analysis predominantly due to age and performance status. Furthermore, of the 229 patients who would have been excluded from the IELSG32 trial entry, only 46 patients (20%) received MATRix, and just five (2%) completed the MATRix regimen at full dose.

We were unfortunately unable to adequately assess the impact of consolidation. Post-induction WBRT was restricted to only 58 (31%) of patients and our study was underpowered to detect a survival difference. MATRix followed by ASCT consolidation is considered by

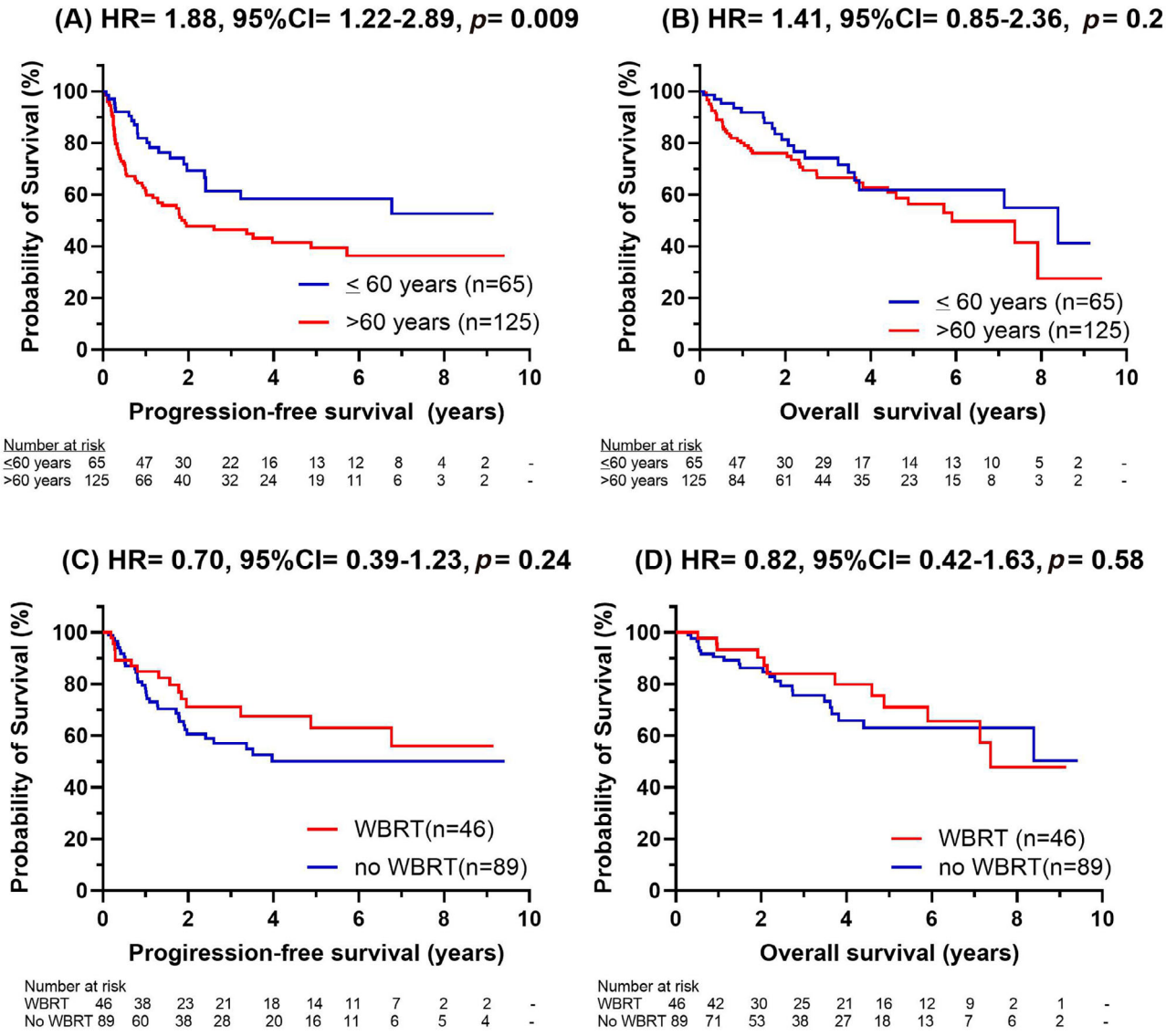

FIGURE 3 Survival graphs. Median follow-up: 3.41 years (0.06–9.42). (A) Progression-free survival and (B) Overall survival by age. (C) Progression-free survival and (D) Overall survival by consolidative whole brain radiotherapy (WBRT) versus no consolidative WBRT (dose 20–45 Gy). Patients who received WBRT for relapsed/refractory disease or consolidative ASCT were excluded from the analysis.

many as a standard of care, but only 15 patients were treated with consolidative ASCT in our cohort, again reflective of the census period [12]. Nonetheless, our findings indicate that good outcomes can be achieved even without consolidative WBRT or ASCT [5]. Proceeding to ASCT after R-MPV is a viable alternative to MATRix [26]. Other strategies such as maintenance HD-MTX after induction chemotherapy or utilizing rationally-directed therapies, such as lenalidomide or BTK inhibitors, remain under investigation, while the Australasian Leukaemia & Lymphoma Group NHL32 study is evaluating the role of pembrolizumab maintenance after MATRix or R-MPV/Ara-C (ACTRN12619000518167, NCT02623010, and NCT04737889) [27].

As demonstrated in our dataset, rituximab is now routinely incorporated into modern regimens and hence it is not possible to discern if it confers an independent survival benefit. The only randomized prospective study designed to evaluate rituximab efficacy in this setting did not demonstrate improved outcomes, but the chemotherapy regimen used (MBVP) was associated with inferior outcomes compared to other studies (1-year event-free survival 49%–52%) [16].

Contrast-enhanced magnetic resonance imaging is used for diagnosis and response assessment [28]. Response rates after completion of HD-MTX chemotherapy in our cohort were encouraging (ORR 72%, CR 50%), but a comparison between cohorts nor Cox regression modeling was possible due to missing data. Furthermore, comparisons were further hindered by inter-observer variability of response assessment, likely due to the challenges of delineating between post-treatment inflammatory changes and residual disease [29]. There is promising data that adjunct positron emission tomography imaging can better distinguish between those in complete response and partial response, but more studies are required and this is incorporated into the current NHL32 study (ACTRN12619000518167) [30].

TABLE 3 (A, B) Cox regression model for progression-free survival and overall survival, respectively. Time from diagnosis to chemotherapy dichotomized 7 days or less versus more than 7 days. Renal impairment was defined as either creatinine clearance (as per the Cockcroft-Gault equation) or estimated glomerular filtration rate (eGFR) < 60 mL/min [22, 23]. For cumulative HD-MTX and HD-MTX-RDI, only patients receiving more than two cycles of HD-MTX were included (see 'methods' section). Response assessments were not included in modeling due to missing data (≥ 20%).

(A) Progression-free survival				
Covariates	**Univariate HR (95%CI)**	***p*-Value**	**Multivariate HR (95%CI)**	**p-Value**
Sex	1.02 (0.67–1.58)	0.919		
Age ≤ 60 years	0.53 (0.33–0.86)	**0.01**	0.56 (0.32–0.99)	**0.045**
ECOG 2–4	1.08 (0.68–1.76)	0.744		
LDH	1.18 (0.75–1.88)	0.475		
Deep structure involvement	0.81 (0.53–1.23)	0.316		
Preserved renal function	0.81 (0.35–1.86)	0.631		
Diagnosis to chemotherapy (days)	0.99 (0.60–1.65)	0.976		
Rituximab	0.54 (0.32–0.92)	**0.024**	1.12 (0.53–2.35)	0.765
MPV/Ara-C versus other chemotherapy	0.39 (0.25–0.61)	**<0.001**	0.40 (0.23–0.69)	**0.001**
HD-MTX cumulative dose	0.9 (0.8–1.1)	0.07		
HD-MTX-RDI > 0.75	0.4 (0.23–0.7)	**0.001**	0.54 (0.31–0.96)	**0.035**
WBRT	0.69 (0.43–1.1)	0.12		
ASCT	0.64 (0.26–1.59)	0.34		
(B) Overall survival				
Covariates	**Univariate HR (95%CI)**	***p*-Value**	**Multivariate HR (95%CI)**	***p*-Value**
Sex	1 (0.61–1.65)	0.999		
Age ≤ 60 years	0.71 (0.41–1.22)	0.21		
ECOG 2–4	1.18 (0.66–2.11)	0.574		
LDH	0.96 (0.53–1.7)	0.888		
Deep structure involvement	0.86 (0.52–1.44)	0.569		
Preserved renal function	0.60 (0.24–1.51)	0.28		
Diagnosis to chemotherapy (days)	0.86 (0.48–1.55)	0.626		
Rituximab	0.66 (0.35–1.24)	0.193		
MPV/Ara-C versus other chemotherapy	0.45 (0.26–0.76)	**0.003**	0.45 (0.24–0.84)	**0.013**
HD-MTX cumulative dose	0.9 (0.78–1.04)	0.116		
HD-MTX-RDI > 0.75	0.28 (0.15–0.53)	**<0.001**	0.34 (0.18–0.65)	**0.001**
WBRT	0.73 (0.42–1.26)	0.263		
ASCT	0.62 (0.19–1.97)	0.42		

Abbreviations: ASCT, autologoust stem cell transplantation; HR, hazard ratio; HD-MTX-RDI, high-dose methotrexate relative dose intensity; LDH, lactate dehydrogenase; WBRT, whole brain radiotherapy.

HD-MTX and Ara-C dosing is dependent on renal function, yet in our cohort renal impairment did not appear to impact survival. This has to be interpreted with caution given only 6% of patients had renal impairment, which was estimated rather than measured via 24-hour urine collection or nuclear medical imaging [22, 23]. Secondly, there is no clear consensus regarding HD-MTX and Ara-C dose adjustment based on renal function, particularly in the 60–100 mL/min range [23, 31].

This study has several limitations inherent to its retrospective nature, of which selection bias is a constant and unmodifiable factor despite robust local registry practices. Incomplete data precluded accurate risk stratification of patients according to IESLG criteria, while ECOG PS was largely estimated retrospectively. The rarity of the disease impacted sample size and statistical power, particularly in the MATRix and ASCT cohorts which were less commonly used during this census period. Finally, we were unable to use a treatment-specific 'estimated' dose for our HD-MTX-RDI calculations due to the response-adapted nature of the MPV/Ara-C protocol as well as the bespoke dosing strategies used in the HD-MTX

monotherapy cohort. Nonetheless, 14 g/m^2 is an established comparator for estimating HD-MTX-RDI [4].

We present data from real-world patients treated at multiple centers over a 10-year period. Sequential, response-adapted approaches can achieve excellent outcomes, even in older patients who are ineligible for a high-intensity concurrent chemotherapy approach (i.e., MATRix) and do not undergo traditional consolidative strategies. These findings support a rationale for using a sequential regimen in select patient groups to attempt greater maintenance of dose intensity and cumulative dose, potentially expanding the pool of patients eligible for consolidative ASCT. There remains a clear unmet need for less toxic and more effective deliverable therapies for older and frailer patients.

AUTHOR CONTRIBUTIONS

Maciej Tatarczuch contributed to the study design, data collection, data analysis, and manuscript preparation. Gareth P. Gregory contributed to the study design and manuscript preparation. All other authors listed contributed to data collection and manuscript preparation.

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Tara Cochrane: Research funding: Beigene. Advisory: Janssen Cilag.

Eliza A. Hawkes: Consultancy/Advisory: AstraZeneca, Janssen Oncology, Merck Sharpe & Dohme, Gilead Sciences, Bristol Myers Squibb, Novartis, Beigene, Link Healthcare, and Regeneron. Speaker's Bureau: Roche/Genentech, Regeneron, and Abbvie. Research funding: AstraZeneca, Celgene, Merck KGaA, Janssen-Cilag, Gilead Sciences, Mundipharma, Bristol-Myers Squibb, and Roche/Genentech. Travel: AstraZeneca.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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