

R-MPV followed by High-Dose Chemotherapy with TBC and Autologous Stem-Cell Transplant for Newly Diagnosed Primary CNS Lymphoma

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Running-head: R-MPV and transplant for primary CNS lymphoma

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Key Points

- We conducted a phase II study in newly diagnosed PCNSL utilizing R-MPV and high-dose chemotherapy with autologous stem cell transplant.
- Excellent disease control and overall survival (2-y PFS: 79%) were observed, with an acceptable toxicity profile and minimal neurotoxicity.

Abstract

High-dose methotrexate-based chemotherapy is the mainstay of treatment for primary central nervous system lymphoma (PCNSL), but relapses remain frequent. High-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) may provide an alternative to address chemoresistance and overcome the blood-brain barrier. In this single-center phase II study, newly-diagnosed PCNSL patients received 5-7 cycles of chemotherapy with rituximab, methotrexate (3.5g/m²), procarbazine and vincristine (R-MPV). Those with a complete or partial response proceeded with consolidation HDC with thiotepa, cyclophosphamide and busulfan (TBC), followed by ASCT and no radiotherapy. Primary endpoint was 1-year progression-free survival (PFS), N=32. The median age was 57; median KPS was 80. Following R-MPV, objective response rate was 97% and 26 (81%) patients proceeded with HDC-ASCT. Among all patients, median PFS and overall survival (OS) were not reached (median follow-up: 45 months). The 2-year PFS was 79% (95%CI 58-90), with no events observed beyond two years. The 2y-OS was 81% (95%CI 63-91). In transplanted patients, the 2-year PFS and OS were 81%. There were three treatment-related deaths. Prospective neuropsychological evaluations suggested relatively stable cognitive functions post-transplant. In conclusion, this treatment was associated with excellent disease control and survival, with an acceptable toxicity profile and no evidence of neurotoxicity thus far. This trial is registered to www.clinicaltrials.gov as NCT00596154.

Introduction

Over 90% of patients with primary CNS lymphoma (PCNSL) display a diffuse large B-cell lymphoma (DLBCL) phenotypic subtype, but standard DLBCL regimens such as CHOP and variations are ineffective in this disease.^{1,2} This has been explained by poor penetration of these agents across the blood-brain barrier (BBB), a problem that has been partially addressed with the development of high-dose methotrexate-based regimens (HD-MTX) that result in therapeutic CNS and CSF levels after rapid infusions of 1.5-8g/m².³⁻⁵ Such high methotrexate doses are made possible with the concomitant use of leucovorin, which prevents bone marrow and systemic organ damage, while limiting rescue of lymphoma cells in the CNS because it has poor BBB penetration. This clever strategy, utilized with or without whole-brain radiotherapy (WBRT), has resulted in remarkable survival improvements, with recent studies reporting median overall survival (OS) of 31-79 months,⁶⁻¹³ as compared to 12 months observed with WBRT alone.¹⁴ In spite of these improvements, early and late relapses remain frequent, and the majority of patients still die from disease.¹⁵

High-dose chemotherapy (HDC) followed by autologous stem-cell transplant (ASCT) has been proposed as an alternative consolidation therapy in PCNSL.¹⁶ In addition to overcoming intrinsic chemoresistance of lymphoma cells, HDC-ASCT may improve disease control by affording higher CNS drug concentrations, circumventing chemoresistance mediated by the BBB- a similar “high-dose/ rescue” paradigm proven successful in the development of HD-MTX. We previously conducted a phase II study in newly-diagnosed PCNSL testing an induction chemotherapy with HD-MTX and cytarabine, followed by consolidation HDC-ASCT utilizing BCNU, etoposide, cytarabine and melphalan (BEAM).¹⁷ Unfortunately, that treatment resulted in suboptimal disease control, with an intent-to-treat (ITT) 3-year event-free survival (EFS) of only 25%, and a 3-year OS of 60%. In the present study, we sought to optimize this strategy by utilizing an enhanced induction regimen consisting of rituximab, methotrexate, procarbazine and vincristine (R-MPV)⁶, as well as a more aggressive, CNS penetrant HDC regimen consisting of thiotepa, busulfan and cyclophosphamide (TBC).¹⁶

Patients and methods

Patients

Immunocompetent adult patients with histologically confirmed newly-diagnosed PCNSL with brain involvement were enrolled in this prospective, single-arm, phase II study between 06/2005 to 09/2011. The online Appendix details inclusion/ exclusion criteria and baseline evaluations. Patients were eligible if they had non-Hodgkin lymphoma (NHL) involving the brain, as demonstrated by MRI, and histologic confirmation by: i) Positive CSF cytology for lymphoma or a monoclonal lymphocyte population defined by cell surface markers, ii) Vitreous or uvea biopsy demonstrating NHL or iii) Brain biopsy. Other inclusion criteria consisted of age 18-72 years, negative HIV-testing, left ventricular ejection-fraction $\geq 50\%$, absence of systemic lymphoma on the chest,

abdomen and pelvis CT and bone marrow biopsy, leukocytes $>3000/\text{mm}^3$, platelets $>100,000/\text{mm}^3$, bilirubin $<2\text{ mg/dL}$, serum creatinine $<1.5\text{ mg/dl}$ or creatinine clearance $>50\text{cc/min}/1.73\text{ m}^2$. Exclusion criteria consisted of prior cranial irradiation or chemotherapy for PCNSL, other active malignancy (exception: skin basal cell carcinoma and cervical carcinoma in situ) or immunodeficiency. Patients were eligible regardless of performance status. Pre-treatment evaluations also included CSF sampling, slit lamp exam, electrolytes, liver enzymes, EBV, CMV, HSV, hepatitis B/C serologies, urinalysis, 24-hour creatinine clearance and chest X-Ray.

The trial and informed consent were approved by the Institutional Review Board (clinicaltrials.gov:NCT00596154). Written informed consent was obtained from all patients or guardians in accordance with the Declaration of Helsinki. Data was analyzed by the authors at Memorial Sloan-Kettering Cancer Center, and all authors had access to primary clinical trial data.

Induction Chemotherapy

Treatment started with an induction R-MPV chemotherapy⁶ (1 cycle=14 days), as follows: Day 1: Rituximab 500 mg/m^2 IV, Day 2: Methotrexate 3.5 mg/m^2 IV (over 2 hours) and vincristine 1.4 mg/m^2 (capped at 2.8mg). Procarbazine $100\text{ mg/m}^2/\text{day}$ was given on days 2-8 during odd cycles. Standard hydration and leucovorin rescue were given per institutional guidelines. To prevent febrile neutropenia and toxic deaths previously observed with R-MPV, prophylactic filgrastim was given to all patients.

An MRI of the brain was performed after 5 cycles. Patients with progressive disease (PD) were taken off-study. Patients with complete response (CR) proceeded directly to HDC-ASCT. Patients in partial response (PR) or stable disease (SD) received two additional cycles, and proceeded with HDC-ASCT if PR/CR was observed on a repeat MRI, or taken off-study if SD or PD. After transplant, patients were followed radiographically, with no WBRT or further treatments offered until progression. Responses were assessed utilizing previously described criteria;¹⁸ in addition to CR, PR, SD and PD, those criteria also characterize unconfirmed CR (CRu), defined by absence of contrast-enhancing disease in the setting of corticosteroids use, or minimal enhancing abnormalities of uncertain significance, typically corresponding to post-operative changes following biopsy.

Harvesting and HDC-ASCT

Peripheral blood stem cell (PBSC) harvesting was performed after the 1st or 2nd R-MPV cycle, or at discretion of treating physician, following institutional standard procedures. Cytapheresis was performed after bone marrow recovery and repeated daily up to day 7 until $>5 \times 10^6$ CD34+ cells were collected (minimum acceptable total yield: 2×10^6 CD34+ cells/kg).

Patients in CR/PR as described above underwent pre-transplant evaluation (Appendix, online); those deemed clinically eligible proceeded with HDC-ASCT with thiotepa 250 mg/m² IV on days -9, -8 and -7; busulfan 3.2 mg/kg IV on days -6, -5 and -4; cyclophosphamide 60 mg/kg IV on days -3 and -2. Stem cell reinfusion occurred on day 0. Supportive therapy followed institutional guidelines, including G-CSF, seizure and infection prophylaxis, hydration, anti-emesis, vitamin K and irradiated blood products.

Response was assessed after R-MPV and prior to transplant, and every 3 months thereafter (first two years), then every 4 months (third and fourth years) and every 6 months thereafter. Repeat CSF and/or ocular exam were done at those time points if CSF or ocular involvement were present at diagnosis.

Exploratory Neuropsychological Testing, Quality of Life and Radiographic Evaluation of Neurotoxicity

In addition to investigators' clinical assessment of neurotoxicity,¹⁹ potential neurotoxic effects of disease, R-MPV and HDC-ASCT were further characterized through prospective neuropsychological and quality of life (QoL) evaluations, as well as radiographic assessment of white matter abnormalities. Evaluations were conducted in progression-free patients at the following time points: pre-treatment (baseline), after induction chemotherapy (before transplant), and at 6-month intervals following transplant. The present analysis reports on evaluations up to 24 months after transplant.

Neuropsychological evaluations were performed in 60-minute sessions. Raw test scores were compared with published normative values according to age and education, and converted into z-scores to characterize presence and severity of cognitive difficulties. A z-score ≤ -1.5 represents impairment. The following tests were performed: Trail Making Test Part-A (TMTA) and Part-B (TMTB); Brief Test of Attention (BTA); Controlled Oral Word Association Test (COWAT), Hopkins Verbal Learning Test-Revised (Total Learning [HVLTR-TL]; Delayed Recall [HVLTR-DEL]; Discrimination Index [HVLTR-DI]), and Grooved Pegboard Test (Dominant Hand [GPTD]; Non-Dominant Hand [GPTND]).

Self-reported QoL and mood were evaluated utilizing the Functional Assessment of Cancer Therapy-Brain Cancer (FACT-BR) and the Beck Depression Inventory (BDI), respectively.

FLAIR MRI sequences obtained at the same time points were scored for white matter abnormalities utilizing the modified Fazekas scale, detailed in Figure 2C.²⁰

Statistics

The primary end-point was 1-year PFS among all patients, defined as time from registration to tumor relapse, progression or death of any cause, whichever comes first.

For the purposes of PFS estimates, patients who withdrew consent or were removed from study because of reasons other than progression, toxicity or death were censored at the date of last radiographic assessment confirming a progression-free status. With a sample size of 33 patients, an exact binomial test with a nominal 0.05 one-sided significance level has 90% power to detect the difference between the null hypothesis (0.5 observed in HD-MTX without radiotherapy¹³) and the alternative proportion of 0.75. The study was to be stopped if more than two toxic deaths occurred among the first 15 patients, or four toxic deaths at anytime. If the true risk of toxic death is $\geq 16\%$, then the probability of seeing 4 toxic deaths (and stopping the trial) was at least 80%. Secondary end-points consisted of OS, acute and chronic toxicities (CTCAEv3), response rate after R-MPV and after HDC-ASCT. Exploratory endpoints consisted of evaluation of neuropsychological, QoL and white matter abnormalities, as above.

Kaplan-Meier methodology was utilized for analysis of OS and PFS. Neuropsychological test scores were summarized using descriptive statistics, and longitudinal trajectories evaluated using linear mixed models (LMMs) controlling for age and estimated IQ. Exact follow-up assessment times from baseline were calculated, and both linear and quadratic terms were estimated by the LMMs. McNemar's chi-square was used to test for significant changes in MRI white matter abnormalities scores between assessments.

Results

Patient characteristics

A total of 33 patients were enrolled and 32 analyzed; one registered patient was excluded because of presence of systemic lymphoma at diagnosis, discovered upon post-hoc radiology review, deeming the patient ineligible. The median age was 57 (range: 23-67) and median KPS was 80 (40-100). Table 1 shows detailed patient characteristics.

Induction Treatment

Induction R-MPV was well tolerated, with no treatment-related deaths and no treatment discontinuation due to toxicity; grades 3 and 4 toxicities are summarized in Table 2. Following five R-MPV cycles, 14 patients were in CR/CRu, 16 in PR, and one progressed (Table 3 and patient flow chart [Appendix, online]). One additional patient had undergone complete resection prior to enrollment and had no measurable disease at baseline; that patient was stable after 5 cycles of R-MPV. All patients in less than CR, in addition to two patients in CR/CRu with incomplete resolution of symptoms after 5 cycles received two additional R-MPV cycles (N=19). The objective response rate after R-MPV, defined as CR, CRu or PR after 5 or 7 cycles in eligible patients with measurable disease (N= 31 evaluable) was 97% (95%CI: 83-100).

HDC-ASCT

Thirty-one (97%) patients were deemed eligible for transplant based on response, which includes the completely resected patient who remained stable following 7 R-MPV cycles. A total of N=26 (81%) patients eventually received HDC-ASCT. The other 5 patients did not undergo transplant because of refusal/ consent withdrawal (N=2) or physician's decision (N=3), and were removed from study. There were no harvesting failures.

Table 4 summarizes toxicities observed with TBC and median times to hematologic recovery. There was no veno-occlusive disease. Two patients died from transplant-related acute complications: a 57 year-old patient developed a Stevens-Johnson syndrome and a 59 year-old patient developed septic shock. Another patient aged 61 developed a fatal chronic colitis of undetermined etiology, potentially representing graft-versus host disease. In that patient, symptoms started three weeks following transplant, and responded poorly to corticosteroids. To date, no patient has developed secondary malignancies.

PFS and OS

Among all patients (N=32), the median PFS has not been reached (Figure 1A) and the 1-year PFS estimate is 82% (95%CI 62-92). There have been no events after two years, and the 2-year, 3-year and 5-year PFS estimates are 79% (95%CI: 58-90). Aside from the toxic deaths, there was no treatment discontinuation due to toxicities, and event-free survival and PFS are identical. The events were toxic deaths (N=3), progression during R-MPV (N=1) and progression after transplant (N=2).

The median OS (Figure 1B) has not been reached and the 1-year OS is 88% (95%CI 70-95). No deaths were observed beyond two years, with a 2-year, 3-year and 5-year OS of 81% (95%CI 63-91). The median follow-up of survivors is 45 months (range: 27-86).

Among the 26 transplanted patients, the 1-year PFS was 85% (95%CI 64-94) and the 2-year, 3-year and 5-year PFS were 81% (95%CI 60-92); the median PFS was not reached (Figure 1C). The 1-year OS is 88% (95%CI 68-96) and the 2-year, 3-year and 5-year OS are 81% (60-92%); the median OS was not reached (Figure 1C).

The effects of age were analyzed according the MSKCC RPA class cutoff of 50.²¹ Patients age \leq 50 tended to achieve superior PFS ($p=0.05$, Figure 1D) and OS ($p=0.06$), with no observed progression or death of any cause.

The outcomes of patients removed from study in spite of being eligible for transplant (N=5) were as follows: Two patients chose to receive high-dose cytarabine and no further treatment; one of those relapsed and received salvage chemotherapy and HDC-

ASCT with TBC. The remainder three patients chose to receive WBRT (2 patients: 23.4Gy, one: 45Gy), and have never relapsed. All five patients remain alive, but as described above, they were censored at the time of last on-study radiographic assessment for the purposes of PFS calculation, and therefore the reported PFS endpoints do not reflect these additional treatments.

Neuropsychological Testing, Quality of Life and Radiographic Evaluation of Neurotoxicity

No clinical neurotoxicity, defined as neurologic deterioration in the absence of disease progression, was reported by treating physicians. In addition, 16 progression-free patients participated in the neuropsychological and QoL evaluations (Figure 2 and Appendix, online).

As shown in figure 2A, at baseline, there was evidence of impairment in several cognitive domains, characterizing baseline disease burden. Results of LMM analysis showed significant positive linear time components (months since baseline) for the HVLT-R-DEL, HVLT-R-DI ($p < 0.05$), indicating continuous improvement in scores from baseline over time. Likewise, all of the other tests had significant positive linear components up to 12-18 months post transplant. However, a significant (TMTA, TMTB, BTA, HVLT-R-TL $p < 0.05$) or marginally significant (COWAT, GPTD, GPTND; $p < 0.10$) quadratic time component was observed, suggesting that the rate of cognitive improvement slowed by 12-18 months post transplant.

Self-reported QoL largely mirrored the improvement of cognitive function in the LMM analysis (Figure 2B). FACT-BR scores significantly improved from baseline, with slowed improvement by 12-18 months post transplant; BDI scores significantly and linearly decreased over time.

Analysis of white matter abnormalities (Figure 2C) showed an improvement after R-MPV, with 81% of patients displaying scores 2-3 at baseline, compared to 19% after R-MPV (McNemar's chi-square $p=0.002$). Following transplant, there was an increase in white matter abnormalities, with 44% of patients with scores 2-3 (McNemar's chi-square $p=0.046$), which then remained stable over time. No scores above 3 were seen at any time.

Discussion

In this phase II study, patients with newly-diagnosed PCNSL were treated with R-MPV chemotherapy, followed by consolidation HDC-ASCT with TBC in responding patients, and no further treatment until progression. Favorable disease control was observed (2-year PFS: 75%; 2-year OS: 81%), far exceeding results of our previous experience with HDCASCT in PCNSL utilizing HD-MTX/ cytarabine and BEAM.¹⁷ Importantly, no clinically significant neurotoxicity has developed to date, and quality of life continuously improved over time.

A number of factors contributed to the favorable results observed in this trial, in comparison to our previous study (Table 5).¹⁷ The induction chemotherapy performed better, with a higher response rate (97%) that increased the number of patients undergoing HDC-ASCT (81%), and minimized disease burden prior to transplant (69%

transplanted in CR). This excellent performance confirms our previous experience with R-MPV,⁶ which seems superior to results with MPV, although it remains difficult to determine the contribution of rituximab, currently being investigated in an ongoing randomized trial. Moreover, the TBC regimen, while more toxic, resulted in improved, durable disease control, likely reflecting higher CNS drug levels in comparison to BEAM.

The TBC regimen was chosen based on favorable results observed in recurrent PCNSL.^{16,22-25} In a multicenter phase II study (N=43),¹⁶ TBC was utilized following a cytarabine/ etoposide (CYVE) salvage chemotherapy, achieving PFS of 12 months and OS of 18 months. Among transplanted patients (N=27), PFS was 41 months. Three patients died from CYVE but there were no transplant-related deaths, which is in line with other studies on TBC in CNS lymphomas^{24,25} and other malignancies,²⁶⁻²⁸ all reporting transplant-related mortality under 5%. In our study, treatment-related mortality appeared higher, but it is difficult to determine if this could be due to a higher susceptibility specific to PCNSL patients, or if it could reflect a less selected patient population, as compared to recurrent disease patients receiving TBC after surviving highly toxic salvage chemotherapies, such as CYVE. Also of interest is the fact that some patients in Soussain's study¹⁶ were transplanted in spite of no response to CYVE, and still survived longer (OS: 9 months) than CYVE-refractory patients who were not transplanted (OS: 5 months). This raises the intriguing question of whether the chemoresistance observed in recurrent CNS lymphoma after induction chemotherapies can be at least in part a consequence of the BBB reducing drug access, which could be overcome by the high chemotherapy doses afforded by transplant-based strategies. This question was not addressed in our study, given that only one patient progressed on R-MPV, and as per protocol design, she did not receive HDC-ASCT.

In addition to our previous study with BEAM, a number of trials have examined the use of HDC-ASCT in newly-diagnosed PCNSL (Table 5). However, interpreting results is difficult because, unlike our trials, a significant proportion of patients in those studies also received WBRT, given either as adjuvant treatment post-ASCT to all patients, or to patients who did not achieve a CR to induction. In a study of 30 patients, methotrexate, cytarabine and thiotepa induction was followed by HDC-ASCT with BCNU/thiotepa, and hyperfractionated WBRT (45 Gy for CR and 50 Gy for PR).^{29,30} The 3-y OS was 69% in all patients, and 87% in transplanted patients. There was no neuropsychological evaluation, but five patients developed clinically defined neurotoxicity. That same group subsequently reported a small series (N=13) using a similar strategy, but without WBRT if a CR was achieved, and the 3-year OS was 77%;³¹ that study has been expanded³² and final results are awaited. In another phase II study (N=25), induction with MTX 3g/m², BCNU, etoposide and methylprednisolone followed by HDC-ASCT (BEAM) and WBRT (30Gy) achieved 3-y EFS of 58% and 3y-OS of 64%. There was no neuropsychological followup, but at least one patient developed neurotoxicity.³³ A study in 28 patients utilized two doses of single-agent HD-MTX, followed by HDC-ASCT (busulfan/thiotepa), and WBRT 45Gy if less than CR. Three of the 9 irradiated patients died from neurotoxicity, for a 2-y OS of 48%.³⁴ Another study focusing on patients with primary and secondary CNS lymphoma of various histologies and previous treatments selected for transplant utilized rituximab combined with TBC as myeloablative regimen,

and found a favorable toxicity profile, with a 2y-PFS of 81%.³⁵ Additional retrospective studies have been reported, adding to anecdotal experience with HDC-ASCT in CNS lymphoma.³⁶⁻³⁹

The lack of clinically detectable neurotoxicity is a favorable aspect of our regimen, but comprehensive neuropsychological evaluations are essential to fully characterize neurotoxic effects that may impair QoL in long-term survivors. In line with previous reports of R-MPV in PCNSL,⁶ results showed marked improvements in cognitive function and QoL following induction MTX chemotherapy, reflecting a decrease in disease burden. Following transplant, neuropsychological test scores remained overall stable, with self-reported QoL continuously improving. However, we found some indications of acute neurotoxicity following TBC, as exemplified by the increase in white matter abnormalities, and a mild, transient decrease in some neurocognitive scores at the first post-transplant evaluation (Figure 2A and online Appendix). Moreover, the rate of cognitive improvement slowed after 12-18 months, and long-term followup is warranted to determine whether this could represent a trend towards development of late-delayed neurotoxicity.

Our study has some limitations. Inclusion criteria allowed for enrollment of patients regardless of performance status, and up to 72 years old, but our oldest patient was 67 and median age was 57, which is younger than the typical PCNSL population enrolled in non-ASCT trials; only 19% of patients had an MSK RPA class III. Therefore, results must be compared against other PCNSL transplant trials (Table 5), rather than non-transplant treatment strategies that are inclusive of a wider population of patients. Moreover, the R-MPV regimen has not been formally tested without a consolidation strategy such as WBRT or HDC-ASCT. Therefore, it is difficult to assess whether such patients with a more favorable prognosis⁴⁰ could have achieved similar results with R-MPV alone and without any consolidation treatment. It is noteworthy that salvage treatments including TBC-based HDC-ASCT^{16,24} or even WBRT^{41,42} are also effective in this population, and will require further investigation. Ongoing study RTOG 1114 is investigating R-MPV with and without reduced-dose WBRT and will provide further data on the relevance of consolidation treatments in newly diagnosed PCNSL. Finally, this was a single-institution trial, and even though we are reporting on the largest number of transplanted patients published to date (Table 5), the sample size remains small, and results need verification in a multicenter, randomized environment.

In summary, we report a prospective trial of HDC-ASCT in newly-diagnosed PCNSL that was associated with excellent disease control, reflecting an optimized induction chemotherapy and a more effective myeloablative regimen. However, acute toxicities, including three toxic deaths, were observed, and longer neurocognitive follow-up is warranted for evaluation of late-delayed neurotoxicity. This treatment should still be considered experimental, and enrollment in randomized trials⁴³ encouraged to establish the ultimate role and optimal timing of HDC-ASCT in the care of PCNSL patients.

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Authorship and Conflict-of-Interest Statements

Conception and design of the trial: A.O, C.H.W., D.D.C., K.S.P. and L.E.A. Collection and assembling of data: A.O. and G.F. Analysis and interpretation of data: All authors
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Table 1: Patient characteristics (N=32)

Median age (range)	57 (23-67)
Age <60	21 (66%)
Age <50	11 (34%)
Median KPS (range)	80 (40-100)
KPS <70	6 (19%)
KPS <50	1 (3%)
Women	15 (47%)
Men	17 (53%)
MSK RPA	
Class I	11 (34%)
Class II	15 (47%)
Class III	6 (19%)
Diffuse large B cell lymphoma	32 (100%)
CSF Cytology*	
Positive	1 (3%)
Suspicious	2 (6%)
Not performed	1 (3%)
Ocular involvement	3 (9%)
Median product of tumor diameters (range)	6 cm ² (0-20 cm ²)

*Conventional cytology; flow cytometry not performed. KPS : Karnofsky Performance Status ; MSK RPA : Memorial Sloan-Kettering Prognostic Score determined by recursive partitioning analysis (I: age < 50; II: age ≥50 and KPS ≥70; III: age ≥50 and KPS < 70).

Table 2: Grades 3 and 4 toxicities reported during R-MPV (N=32).

Toxicity	Grade 3		Grade 4	
	Number	Percentage	Number	Percentage
Hemoglobin	6	18%		
Neutrophils	6	18%	1	3%
ALT and/or AST	14	42%	3	9%
Creatinine	5	15%		
Infection	4	12%		
Peripheral neuropathy	2	6%		
Fatigue	2	6%		
Thrombosis/ Embolism	1	3%	2	6%
Constipation	1	3%		
Syncope	1	3%		
Encephalopathy			1	3%

Table 3: Response status after R-MPV and following transplant.

	CR/CRu	PR	SD	PD
Response after 5 R-MPV cycles (N=32)	14 (44%)	16 (50%)	1* (3%)	1 (3%)
Best Response to R-MPV induction chemotherapy (5 or 7 cycles) (N= 32)	21 (66%)	9 (28%)	1* (3%)	1 (3%)
Pre-transplant response status in the transplanted patients (N=26)	18 (69%)	7 (27%)	1* (4%)	0 (0)
Best response after transplant (N=26)	21 (81%)	3 (11%)	1* (4%)	1 (4%)

*This one patient had no measurable disease at start of R-MPV due to complete resection. That patient remained stable after 7 cycles of R-MPV and underwent HDC-ASCT. This patient was considered non-evaluable for objective response rate assessment.

CR: complete response, Cru: unconfirmed complete response; SD: stable disease; PD: progressive disease; R-MPV: rituximab, methotrexate, procarbazine and vincristine.

Table 4: Number of patients experiencing grades 3-5 toxicities from transplant, and time to hematologic recovery (N=26).

Non-hematologic	Grade 3		Grade 4		Grade 5	
Febrile neutropenia	11	42%				
Infection	4	15%	2	8%	1	4%
Skin rash	1	4%	1	4%	1	4%
Chronic colitis					1	4%
Encephalopathy	1	4%				
Dehydration	1	4%				
Cardiac failure	1	4%				
Weight loss	1	4%				
Nausea	1	4%				
Diarrhea	1	4%				
Mucositis	1	4%				
Engraftment						
Median time to neutrophil recovery (> 500/mm ³): 9 days (Range: 7-15)						
Median time to platelet recovery (> 25,000/mm ³): 15 days (Range: 10-124)						
Median duration of hospital admission for HDCASCT: 26 days (Range 20-90)						

Table 5: Trials or case series (20 or more patients) reporting outcomes in newly-diagnosed PCNSL patients treated with consolidation HDC-ASCT after methotrexate-based initial treatment.

Ref	N	Induction regimen	ORR to Induction	HDCASCT regimen	Received consolidation HDCASCT	Received consolidation WBRT*	ORR to HDC-ASCT	Med F/u	ITT 3-y PFS	ITT 3y-OS
Regimens including WBRT to all patients										
Illerhaus, ²⁹ 2006	30	MTX 8g/m ² , Ara-C, thiotepa	80%	BCNU, thiotepa + WBRT	23 (77%)	21 (70%)	100%	63m	na	69%
Colombat, ³³ 2006	25	MTX (3g/m ²), BCNU, VP16, methylpred	84%	BEAM + WBRT	17 (68%)	24 (96%)	100%	34m	58%	64%
Regimens with WBRT to patients achieving less than a CR										
Montemurro, ³⁴ 2007	28	MTX 8g/m ²	61%	Busulfan, Thiotepa + WBRT if no CR	16 (70%)	8 (29%)	69%	15m	45%	48% (2y)
Regimens without WBRT										
Abrey ¹⁷ , 2003	28	MTX 3.5g/m ² , Ara-C	57%	BEAM	14 (50%)	0	77%	28m	25%	60%
This study	32	MTX 3.5g/m ² , rituximab, procarbazine, vincristine	97%	Thiotepa, busulfan, CTX	26 (81%)	0	92%	45m	79%	81%

*Number of patients who received WBRT as part of initial treatment, in the absence of tumor progression
 ORR: Objective response rate; HDCASCT: High-dose chemotherapy with autologous stem cell transplant, Med F/u: median follow-up; ITT: intent-to-treat; PFS: progression-free survival; OS: Overall survival; CTX: Cyclophosphamide; VP-16: Etoposide; Ara-C: Cytarabine; MTX: Methotrexate; BCNU: Carmustine; methylpred: methylprednisolone; BEAM: carmustine, etoposide, cytarabine melphalan; WBRT: Whole brain radiotherapy; na: not available

Figure Legends

Figure 1: Progression-free survival and overall survival.

A: Progression-free survival, all patients (N=32); B: Overall survival, all patients (N=32); C: Progression-free and overall survival in transplanted patients; D: Progression-free survival according to age (above 50 versus 50 and under); $p=0.05$.

Figure 2: Neuropsychological testing (A), mood / quality of life scores (B) and evaluation of white matter changes on MRI (C) over time.

Time point 1: Baseline; 2: After R-MPV and before transplant; 3, 4, 5, 6: Every 6 months after transplant.

A: Neuropsychological testing (z-scores) boxplot. BL- baseline; R-MPV- after induction chemotherapy; TMTA-Trail Making Test Part A; TMTB-Trail Making Test Part B; BTA- Brief Test of Attention;COWA: Controlled Word Association Test; HVLT-R-TL: Hopkins Verbal Learning Test-Revised- Total Learning; HVLT-R-DEL: Hopkins Verbal Learning Test-Revised - Delayed Recall; HVLT-R-DI: Hopkins Verbal Learning Test-Revised-Discrimination Index; GPT-D- Grooved Pegboard Test-Dominant Hand; GPT-ND-Grooved Pegboard Test-Non-Dominant Hand. Z-scores ≤ 1.5 represent impairment. The lower and upper boundaries of each box represent the 1st and 3rd quartiles (i.e., the 25th and 75th percentiles), respectively, at the indicated time point, and the inter-quartile range (IQR) is the distance between the lower and upper boundaries. The error bars ("whiskers") extend from the 1st and 3rd quartiles to the lowest and highest scores that are within $1.5 \times \text{IQR}$ of their respective quartile. Any scores beyond the error bars are considered outliers and are represented as individual points. The asterisks represent the median scores. The lines connecting the medians over time for each test have no statistical interpretation and are intended to serve as visual aids.

B : Beck Depression Inventory and FACT-BR (raw scores) boxplot. BDI-Beck Depression Inventory; FACT-BR-Functional Assessment of Cancer Therapy-Brain Cancer. See Figure 2A for boxplot explanation.

C : White matter abnormality scores (modified Fazekas scale) over time (N=16). Fazekas scores: 0- No white matter abnormality; 1- Minimal patchy white matter foci; 2- Start of confluence of white matter disease; 3- Large confluent areas; 4- Confluence of white matter abnormalities with cortical and subcortical involvement; 5- Diffuse leukoencephalopathy. No patient developed white matter abnormality scores of 4 or 5.

Fig.1

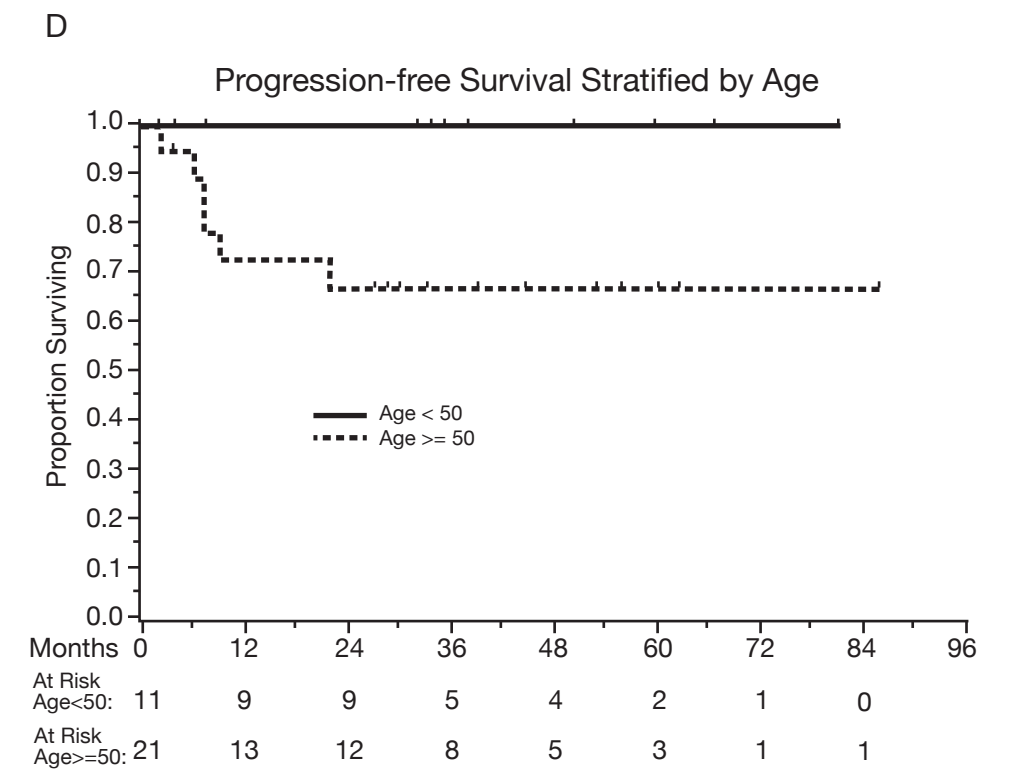
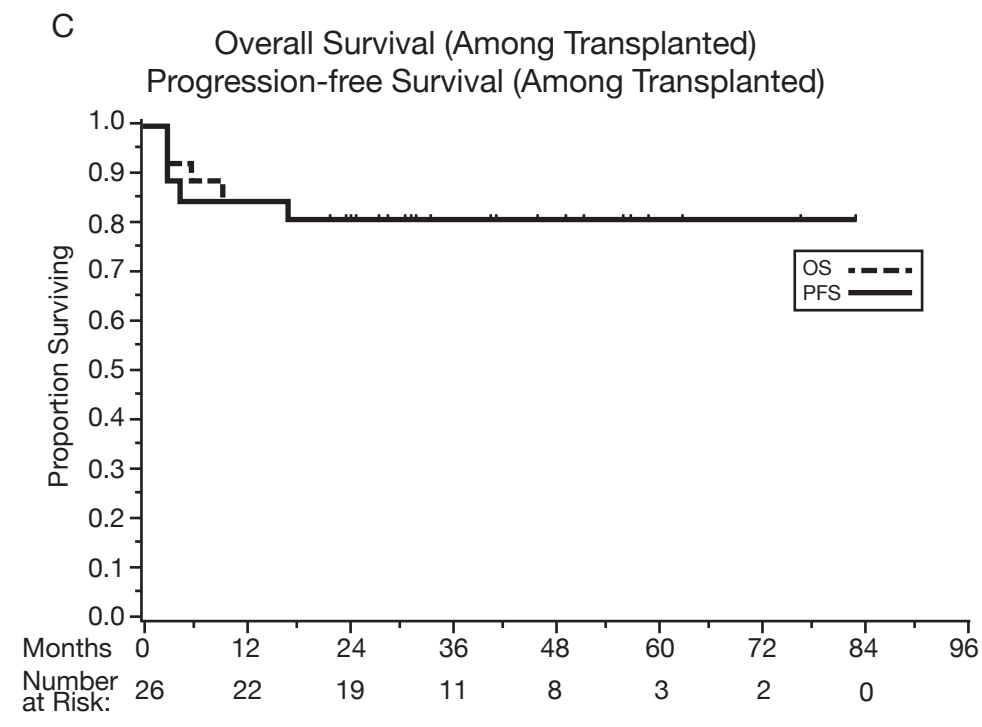
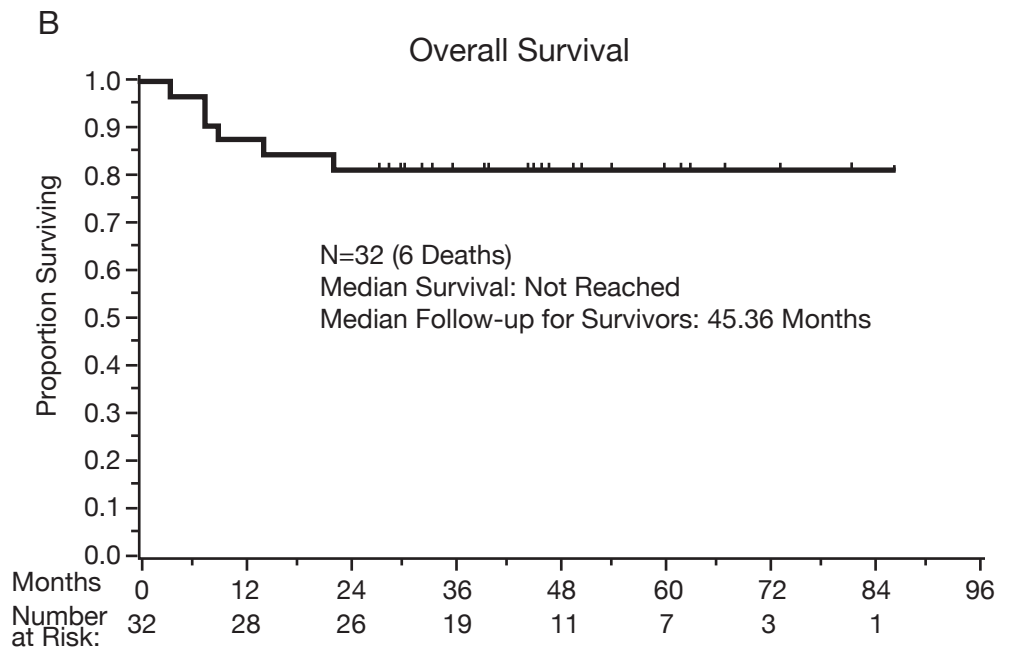
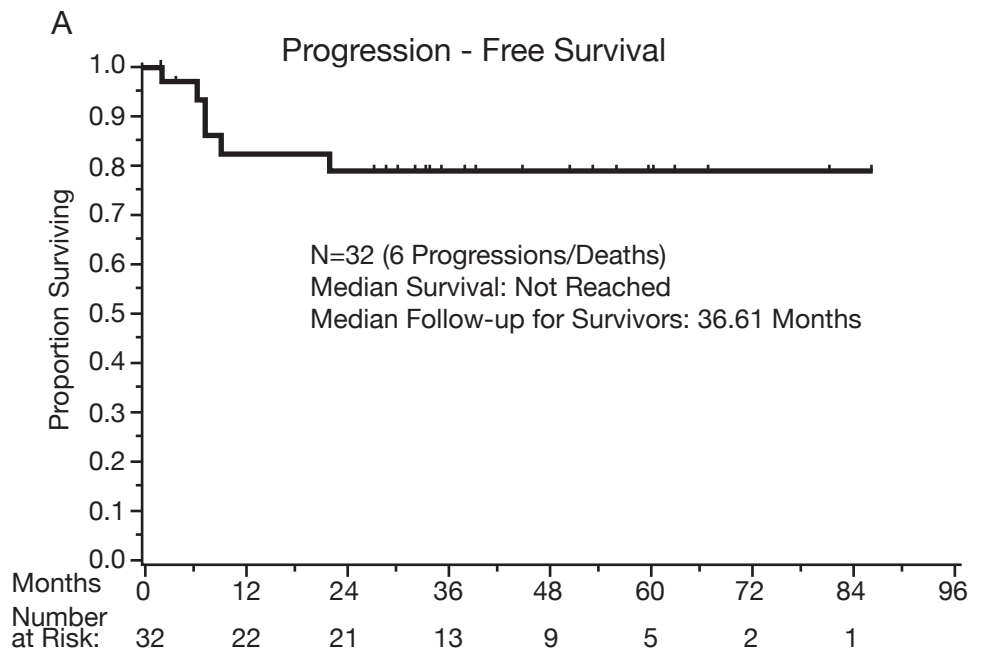
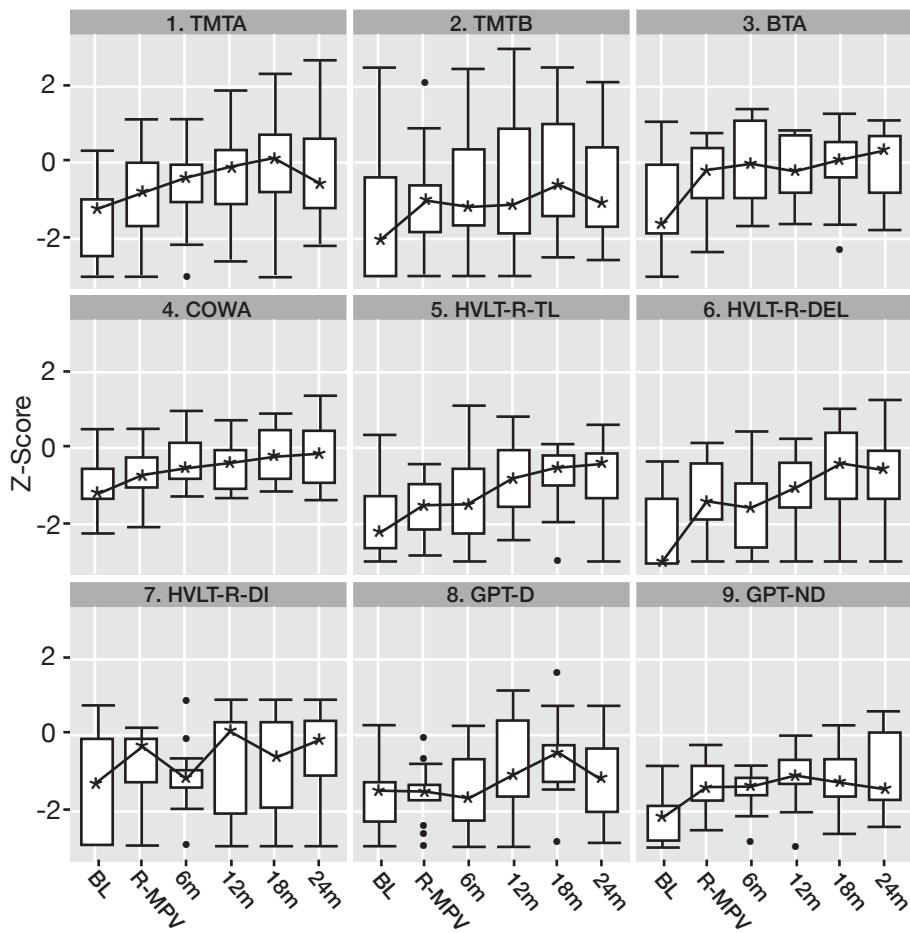
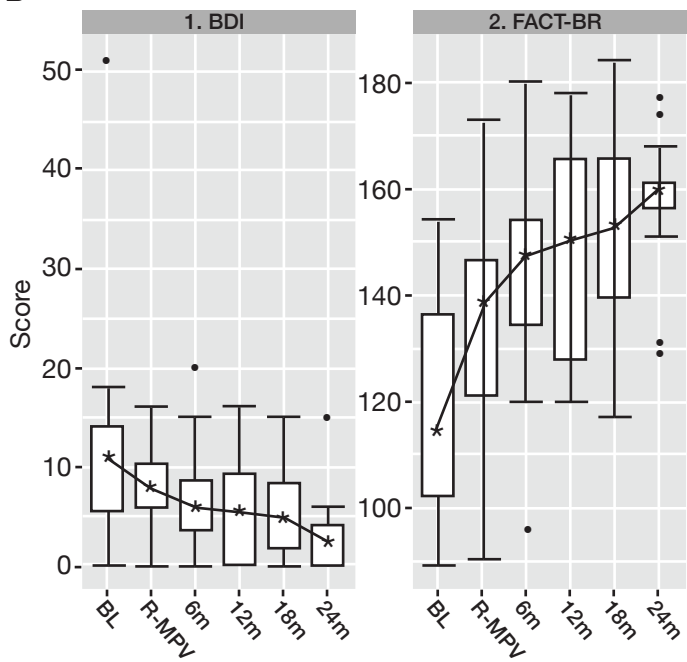


Fig.2

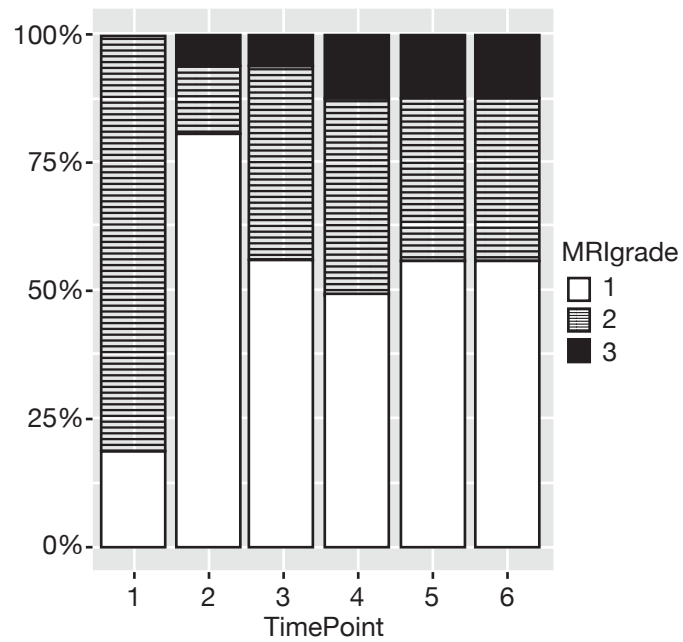
A



B



C





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R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma

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