

Monotherapy with methotrexate for primary central nervous lymphoma has single agent activity in the absence of radiotherapy: a single institution cohort

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Received: 27 October 2009 / Accepted: 30 November 2009 / Published online: 18 December 2009
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Abstract We have retrospectively reviewed toxicities and response of a cohort of primary central nervous system lymphoma (PCNSL) patients treated with high dose parenteral methotrexate (MTX) monotherapy without whole brain radiation. From The Massachusetts General Hospital (MGH) Cancer Registry, active since 1946, we selected all immunocompetent patients with histologic and/or radiographic PCNSL diagnosed between 1980 and 2007. We identified the recipients of MTX with leucovorin rescue as sole therapy. No patient received radiation therapy (XRT). We analyzed this cohort for toxicity, response and patterns of recurrence. The cohort of 121 patients received on average 11 cycles of intravenous MTX at a median dose of 8 g/m². Median interval between cycles was 10 days. After 3 months of therapy, the overall response rate was 85% (58% CR, 27% PR). The overall survival (OS) for the cohort was 7 years and progression-free survival (PFS) was 3.14 years. A trend toward a higher PFS was seen in patients who continued to receive MTX (3.48 years) every three months as compared

to patients who ceased MTX after one year (2.86 years). Of 68 patients who achieved initial CR, there were 40 recurrences. Twenty-six of the 40 were re-induced with MTX as above; Sixty-nine percent again achieved CR. Eighty-one treatment-related toxicities occurred in 1316 MTX cycles. These toxicities included MRI white matter changes ($N = 8$) and lead to MTX cessation in 16 patients. High-dose MTX monotherapy of PCNSL is well-tolerated and provides PFS of >3 years and OS >7 years.

Keywords Methotrexate (MTX) · PCNSL · Chemotherapy · Lymphoma

Introduction

The rise in prevalence of primary central nervous system lymphoma has provided the base for accrual to novel therapies as well as evidence-based treatment options. In general, over half of primary central nervous system lymphoma (PCNSL) patients achieve complete response therapy with overall survival exceeding two years [1]. Anti-folate agents, developed at the NCI in the 1960's, demonstrated activity in tumor cell screening assays [2, 3] and in treatment of systemic B cell lymphoma [4–6]. Methotrexate (MTX) was adopted to treat PCNSL as unlikely to cause significant myelosuppression or white matter toxicity [7]. Its benefit could be seen with deferred radiotherapy (XRT). Parenteral MTX was provided either as two or more cycles prior to XRT [8, 9] or in combination with other agents [10]. Intent-to-treat studies utilizing single agent MTX were performed by the consortiums NABTT [11] and NOA [12, 13] and evaluated in the elderly [14]. The NABTT and meta-analyses that have been performed underscore MTX benefit with CR rates in

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excess of 50%; while the NOA study did not. We have retrospectively reviewed our single institution experience in treating PCNSL. These data serve as a baseline against which future therapeutic strategies can be compared.

Methods

Cohort ascertainment

The Massachusetts General Hospital Cancer Registry since 1946 records all newly confirmed malignant tumors diagnosed. These data are archived in an IRB-approved database and an electronic medical record system. We queried this database for records of patients with PCNSL treated at the Massachusetts General Hospital (MGH) between January 1, 1980 and August 1, 2007. We included non-Hodgkin's lymphoma ("Large-cell lymphoma", "immunoblastic lymphoma" and "NHL of nervous system") [15] of the central nervous system confirmed by pathologic examination. Pathologic diagnoses were not re-confirmed. All patients had mass lesions (MRI) of brain, ventricles or meninges in the setting of pathologic confirmation of lymphoma of brain parenchyma, CSF, nerve roots and/or spinal cord, or clonal immunoglobulin gene rearrangement [16], flow cytometry, or cytologic ("atypical" or "suspicious" or "malignant") abnormalities of cells from CSF or vitreous. We included patients with confirmed involvement of brain, CSF, nerve or spinal cord, in the setting of previous intraocular lymphoma (PIOL), as well as PCNSL patients who later relapsed in brain or CSF. We excluded patients lacking histologic confirmation, immunocompromised patients; those with HIV positivity or recipients of organ transplant, those with CNS low-grade lymphoma or acute leukemia, systemic lymphoma (NHL) with spread to the central nervous system. We recorded comorbidities.

Treatment

Of 209 PCNSL patients we selected 121 whose first therapy was HD-MTX every ten-14 days [11, 17]. Of these 67 have been the subject of reports [7, 9, 11]. We excluded those with multi-drug chemotherapy that was MTX-based; recipients of ≥ 5 standard fractions of whole-brain irradiation (WBXRT) or recipients of alternative dosing schedules of MTX. Prior to 1995, MTX was provided to nine patients at dose level 3.5 g/sq.m. Thereafter dosing was 8 g/sq.m. every ten to fourteen days until disease progression or CR. A subgroup of CR patients continued to receive MTX every month for three cycles and then every three months thereafter ("maintenance"). MTX dosing for all patients was adjusted to pre-treatment calculated or measured glomerular filtration rate. Leucovorin calcium rescue (25 mg every 6 h) was initiated 24 h after the start

of MTX infusion and continued until 24 h after MTX levels fell below $<.25$ mcM/l. No complete responder received further corticosteroids.

Outcome measures

We sought to determine the benefit of MTX therapy for PCNSL of brain. We defined the date of progression as the date (after CR or PR) of provision of the next form of systemic chemotherapy. These treatments at recurrence included retreatment with MTX (systemic MTX, or alternative route MTX: intrathecal, intravitreal, "intraocular"), drugs other than MTX, radiation therapy (to whole brain or localized radiosurgery [SRS] or spine). All 121 patients had radiographic measurable disease. Case ascertainment is depicted in Fig. 1.

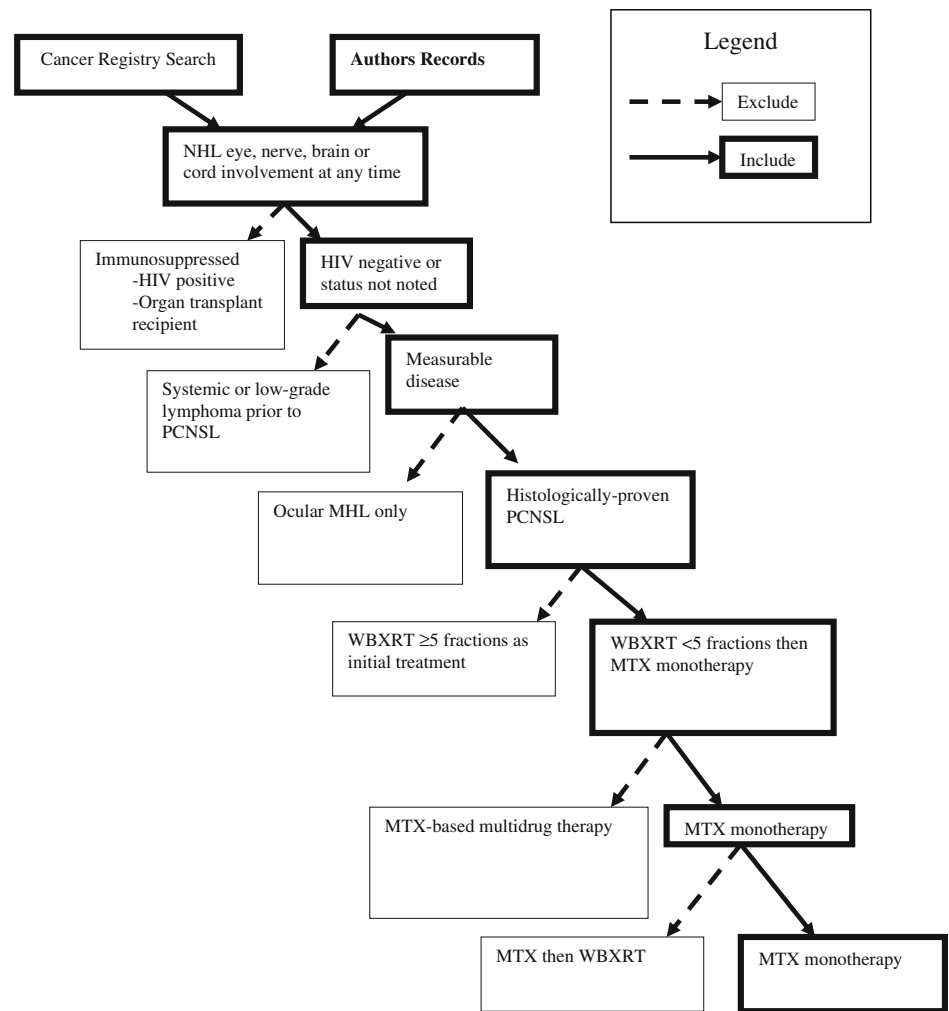
Toxicity

We recorded adverse events that resulted in delay, reduction or cessation of MTX therapy. These included $>$ grade 2 CTC toxicities (NCI toxicity criteria), leukoencephalopathy (in the absence of gadolinium-enhancing tumor); leukopenia (White blood cell count $\leq 3,000$ or ANC $\leq 1,500$); thrombocytopenia (Platelet counts $\leq 75,000$); azotemia (Creatinine $\geq 1.5 \times$ ULN); anaphylactic reaction or generalized eruption; hepatic dysfunction (SGOT or Alkaline phosphatase elevation $>2.5 \times$ ULN); or newly appearing changes in cognition or sensation. We defined leukoencephalopathy $>$ grade 2 (moderate increase in subarachnoid space (SAS); and/or moderate ventriculomegaly; and/or focal flair or T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum) and identified patients with 10% decrement in Mini-mental status exam as performed every two weeks prior to CR and every two months thereafter).

Response to therapy

Response to therapy, based upon two-dimensional measurements of gadolinium enhancing mass(es) on MRI or CT (if MRI contraindicated) at bi-monthly intervals included: Complete response ([CR]—complete absence of gadolinium enhancing mass(es)), Partial response ([PR]—less than complete reduction of enhancing mass(es)), Mixed response ([MR]—variable change of multiple masses including progression with concomitant PR or CR), Stable disease ([SD]—No change in size of a mass), Progressive disease ([PD]—increased diameter of enhancing gadolinium mass(es)). Persisting enhancement at the prior biopsy site was not viewed as progression. We recorded the date of best response after start of MTX as well as the sites of failure.

Fig. 1 Schematic of case ascertainment. *NHL* non-Hodgkin lymphoma, *dx* diagnosis, *IOL* intra-ocular lymphoma, *PCNSL* primary central nervous system lymphoma, *CHT* chemotherapy, *MTX* methotrexate, *WBXRT* whole-brain radiation therapy



Data analysis

We recorded patient age, gender, annualized risk of PCNSL, patient comorbidities, drug toxicities and response to therapy. Patients were not contacted and thus we recorded the interval from diagnosis to last follow-up. Patients lost to follow-up after Cycle 1 MTX, were assigned survival of “zero” months. Their toxicity data were recorded. We calculated progression-free survival (PFS) and overall survival (OS) for all patients.

Results

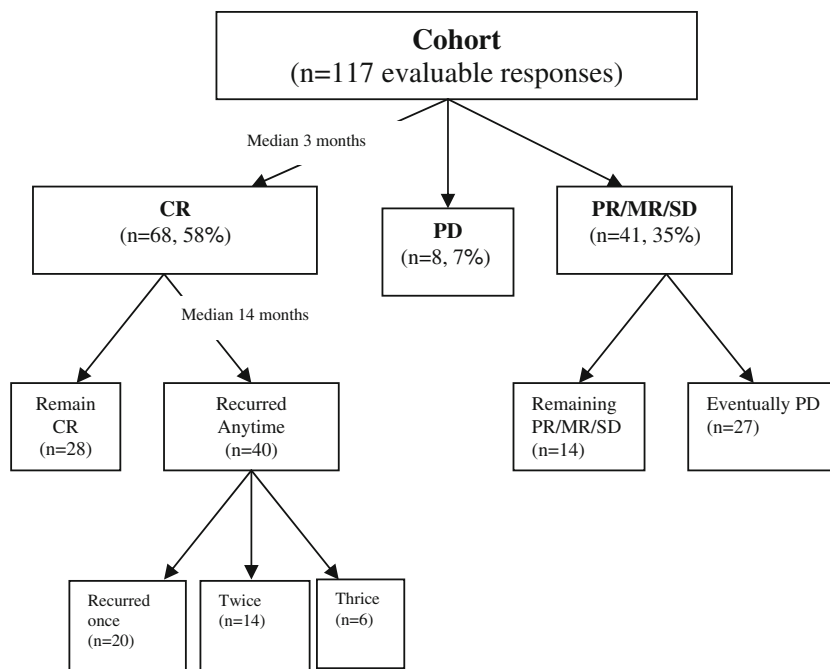
209 patients were diagnosed with primary central nervous system lymphoma between January 1, 1980 and August 1, 2007. The case-incidence peak occurred 1996–2000. One

hundred twenty-one patients received MTX monotherapy, of whom 117 had data for survival evaluation (Fig. 2).

Demographics

The median age of the 121 patients was 63 years (range 23–86 years). Males predominated (53%). Brain parenchymal involvement was most common (94%) including 11% with brain and another nervous system site. Six percent of patient had CSF involvement with nodular measurable disease. Comorbidity included: lupus erythematosus prior MTX therapy (one for “breast cancer” and one for unconfirmed “ocular lymphoma”), renal insufficiency (2), idiopathic thrombocytopenic purpura (2), polyglandular autoimmune syndrome E type 1 (1), steroid use (10), non-brain radiation therapy for systemic malignancy (3) and ocular lymphoma [4], prior chemotherapy (7) and Lyme disease (2).

Fig. 2 Responses to MTX monotherapy. CR complete response, PD progressive disease, PR partial response, MR mixed response, SD stable disease



Response to therapy

Of 121 patients, 106 (87.6%) initially received MTX at a dose of 8 g/m² and fifteen (12.4%) received doses of 3.5 g/m² or less. Response was not evaluable in four patients due to: missing MRI (1 patient), lost to follow-up (1), cessation of MTX prior to response evaluation (2). An additional patient, evaluable for response, died of progressive lymphoma prior to MTX therapy. The overall response rate to Methotrexate induction was 85% (100/117). CR occurred in 58% (58.5% of patients treated at MTX 8 g/m² and 50% at MTX 3.5 g/m²). CR was achieved after a median of 6 cycles of therapy over an elapsed time of 3 months. Twenty-seven percent of patients had PR, 7% PD, 5% SD, and 3% MR. Patients who did not achieve a CR rapidly progressed. Twenty-seven of the 41 patients who achieved PR, SD or MR, progressed after two more cycles of MTX (one month) (Fig. 2).

Six PCNSL patients had MRI measurable tumor in the setting of CSF with “atypical” or “suspicious” cells. Five of these achieved CR (2–9 cycles MTX), and one progressed (1 cycle). Three patients additionally received at least one cycle of intrathecal therapy and five received intravitreal therapy.

The median overall survival (53 deaths and 68 censored) was 7 years (95% CI of 4.6, 12.8). The survival rates at 1, >5 and 10 years were 86, 58 and 44% respectively (Fig. 3, OS). For patients achieving CR, the median progression-free survival was 3.14 years (95% CI of 2.48, 5.18) (Fig. 4, PFS). Thirty percent of the entire cohort progressed during therapy with MTX (Table 1). Forty

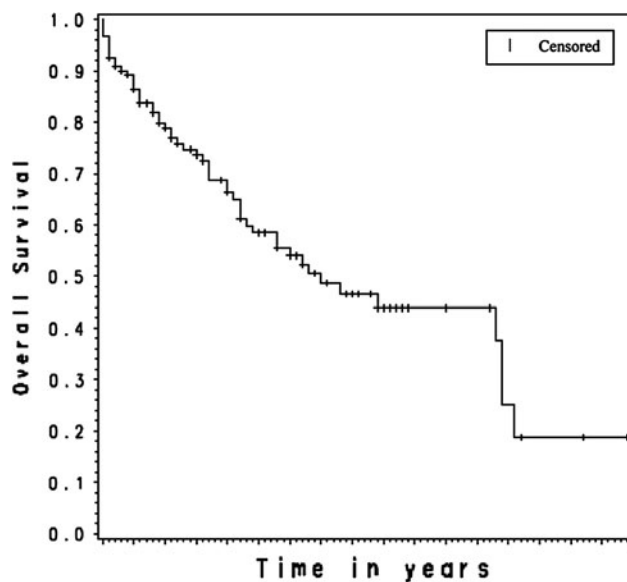


Fig. 3 Overall survival of cohort ($n = 121$). Of 121 patients in the cohort, 53 patients died and 68 survived. The median OS was 7 years with 95% CI 4.6, 12. The 1, 5 and 10 year OS rates were 86, 58 and 44% respectively. *TTP* time to progression, 95% CI 95% confidence interval

additional patients (59% of those with CR) recurred 14 months (IQR 6.75, 32.5) after complete response. Patients in CR who continued MTX at least one year further fared better than those who stopped within two cycles of CR. Progression-free survival for the former was 3.48 years (95% CI of 2.16, 5.8; Fig. 4), versus 2.86 years (95% CI of 1.32 and upper bound not reached; Fig. 4) for

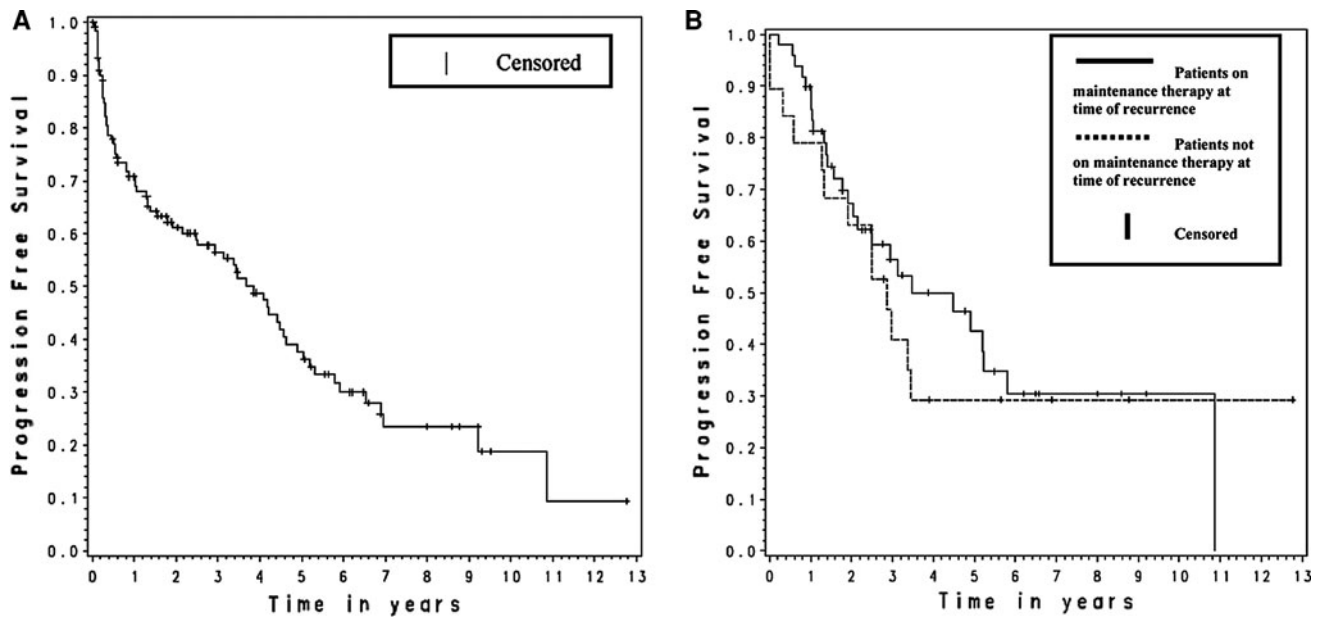


Fig. 4 Progression-free survival. **a** PFS of CR patients ($n = 68$)—Of 68 patients achieving CR, forty progressed, while 28 (censored) remained progression-free. The median PFS was 3.14 years with 95% CI of (2.48, 5.18). The 1, 5 and 10 years PFS rates were 87, 51 and 38%, respectively; **b** PFS by MTX continuation after CR—For patients who ceased MTX within two cycles of CR (dotted line), the

median PFS is 2.86 years with 95% CI of (1.32, upper not reached). The 1, 2 and 5 years rate are 79, 63, and 29% respectively. For patients who continued MTX after CR (solid line), the median PFS is 5 years with 95% CI of (3, 9.2). The 1, 2 and 5 years rate are 90, 67, and 43% respectively. PFS progression-free survival; 95% CI 95% confidence interval

Table 1 Recurrence after MTX therapy ($n = 117$)

Refs.	No.	Dose MTX g/m^2	Frequency	Cycles to response	CR (%)	PD/SD (%)	PFS (months)	OS (months)
[12]	37	8	Biweekly	6	29.7	37.8	13.7	25
[14]	10	8 then 3.5	Every 14 days, 3 cycles	9	60	10	18	20
[23]	20	8 then WBXRT	q 14–21 days	2	50	25	N/a	N/a
[41]	23	8	q. 14 days then WBXRT				6 ⁺	17 ⁺
[42]	4	400 μg (intravitreally)	q. 2 weeks	Median 7	100	0		
[43]	28	100 mg/kg over 3h	Then WBXRT		11	21		

PD progressive disease, CR complete response, MTX methotrexate, IQR inter-quartile range

the latter. Recurrences occurred in brain (68%), vitreous (5), systemic sites (5), nerve root (2) and CSF (1). Of sixty-three deaths (through August 1, 2007), 63% resulted from PCNSL. No deaths were attributable to drug toxicity.

Of CR patients, 40 ultimately recurred including twenty patients with one recurrence, fourteen with two sequential recurrences, and six with three recurrences. Twenty-six patients with relapsed PCNSL were treated again with MTX monotherapy. Eighteen (69%) again achieved CR and one achieved PR.

MTX-toxicities included eighty-one events. Sixteen of these led to drug cessation and 14 to MTX dose reduction or delay. Toxicities included leukoencephalopathy (8) (including full-scale IQ decrement by 30 points which led to MTX cessation); reversible azotemia (21 patients) (of which four led to MTX cessation and three to dose delay or

Table 2 Literature reports of MTX monotherapy

Recurrences	Number of patients (% of entire cohort)
Pts with PD at any time	35 (29.9%)
<i>Patients recurring</i>	
Once	20%
Twice	14%
Three times or more	6%
<i>CRs who recurred</i>	
Median time from CR to recurrence	14 months
Recurrence while receiving MTX	27 of 49 patients
Recurrence while NOT receiving MTX	13 of 19 patients

Ref reference, MTX methotrexate, iv intravenous, WBXRT whole-brain radiation therapy, CR complete response, PD progressive disease, SD stable disease, PFS progression-free survival, OS overall survival, FU follow-up

Table 3 Literature reports of PFS/OS for MTX-based multidrug chemotherapy

Refs.	No.	Treatment	OS (months)	PFS (months)	Neuro-toxicity
[24]	28	MTX, ARA-C and 14 pts received CCNU, ARA = C, and melphalan with stem-cell rescue	Not yet reached (median FU: 28 months)	5.6 (14 pts without transplantation) and 9.3 (14 pts with transplantation)	None
[25]	50	MTX, BCNU, PCZ, methylprednisolone, ARA-C	14.3 (95% CI, 6.2–42)	10.6	6 pts
[26]	74	MTX, dexamethasone and CPA or VP-16; PCZ in addition (for 44 patients)	40.7	77.4 for pts <60 yo 18 months for pts >60 yo	Reversible neuro deficit (7), stroke (5), seizures (1), cerebral herniation (1), death w/in 30 days (4)
[27]	52	MTX, VCR, PCZ then WBXRT then ARA-C (22 without XRT)	60	FU duration too short	13 pts
[28]	39	MTX, CPA, PCZ	41	–	None
[29]	14	MTX, Thio, VCR, dexamethasone, i.i.t. ARA-C	Not yet reached	16.5	13 events
[30]	19	MTX, VCR, PCZ or MTX, VCR, PCZ, ARA-C or MTX, Thio	30.5	Not yet reached	1 pt
[31]	65	MTX, ARA-C, Dex, VCR, ifos, CPA, prednisolone	50	21	2 pts with cog dysfunction, 20 with MRI white matter lesions, 11 with peripheral neuropathy, 6 deaths
[32]	64	MTX, CCNU, PCZ, methylprednisolone, ARA-C	Not yet reached (54 month median FU)	13	6 pts
[33]	23	MTX, Temo	35	8	None
[34]	102	MTX, VCR, PCZ, WBXRT then ARA-c	36.9	24	4 pts, 12 of 82 receiving XRT
[35]	112	(1) WBXRT; (2) MVP; (3) proMACE-MOPP; or (4) R-MTX	24	16	–
[36]	52	MBVP and RT	46	–	1 pt
[37]	54	HDMTX, CCNU, PCZ; or HDMTX, dex (and Ifos, ARA-C)	41.4	9	14 pts (some received WBXRT)

Ref reference, *FU* follow-up, *PFS* progression-free survival, *OS* overall survival, *(HD) MTX* (High-dose) methotrexate, *(WB) XRT* whole-brain radiation, *RT* radiation therapy, *R-MTX* radiation with methotrexate, *ARA-C* cytosine arabinoside, *BCNU* carmustine, *CCNU* lomustine, *dex* dexamethasone, *PCZ* procarbazine, *Thio* thiotepa, *Temo* temozolamide, *VP16* etoposide, *proMACE-MOPP* prednisone, methotrexate, adriamycin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine, *MVP* mitomycin, vinblastine, cisplatin, *MBVP* methotrexate, teniposide, carmustine, methylprednisolone, *CI* confidence interval, *yo* years old

reduction). MTX was continued in four patients despite elevated liver enzymes (LFT) including one MTX delay. The 18 occurrences of leukopenia led to drug cessation (1) dose delays (2) while thrombocytopenia (16) did not. Sixteen cutaneous drug reactions, included a fixed drug reaction, did not require discontinuation; but one anaphylactic reaction led to drug cessation. Nine patients ceased MTX therapy as a result of sepsis (2), renal failure (2), mucositis (2), pulmonary emboli, clostridium gastroenteritis and drug-resistant tachycardia.

Discussion

We report a single-site cohort provided MTX monotherapy for PCNSL. The therapy provided CR or PR response in 85% and PFS of 3.14 years. The overall survivals of 86% at one year, 58% at five years and 44% at 10 years- are likely low as we assumed death to have occurred on the date of last follow-up. These data will well serve investigators describing the benefits to PCNSL patients of novel immunologic or stem cell therapies. Despite initial MTX responses (CR, PR, MR, SD); 30% of the 117 patients progressed within 15 months. We were unable to establish, as has been reported by Ferreri [18], a metric to separate eventual responders from non-responders despite evaluating (unpublished) the prognostic roles of demography, number and volume of brain lesions, pre-therapy performance status and MTX pharmacokinetics. Recent studies [19] suggest correlates of MTX efficacy and toxicity including pharmacogenomic analyses as well as assays of the expression of folate carrier channels [20, 21].

Toxicities of MTX were rare and reversible. Sixty-eight percent of recipients experienced no toxicity; but seven MTX-related toxic events led to MTX cessation. These included: leukoencephalopathy, azotemia, leucopenia, anaphylaxis, sepsis, and mucositis. This low rate reflects care provided by neurologic and chemotherapy nurses with experience in the provision of hydration in the setting of brain edema, the knowledge of drug-MTX interactions and experience in the provision of “accelerated” calcium leucovorin emerging during azotemia or the release of MTX from “third-spaces”. These toxicities have been well documented [22].

Our CR rate of 58% is similar to other reports (Table 2) including Watanabe [23] (CR = 50%) and Ng [14] (CR6/10); but unlike that of Herrlinger [13] (CR = 30%). Uncertain is whether differences reflect the comorbidity of patients or intricacies of MTX administration.

Three months after starting MTX therapy patients can be declared “responders” or “non-responders”. By this evaluation (6 cycles MTX) CR was identified in 58% of patients; PD was declared somewhat earlier (2 months).

Thus 3 months of MTX therapy represents a baseline against which investigators may evaluate the efficacy of adding other agents. MTX—monotherapy is not curative. Progression of disease was seen in sixty-six percent of patients with PR, MR or SD and in 59% of those with CR. Uncertain is whether continuation of MTX-monotherapy prolongs PFS. The PFS for CR patients who continued MTX every three months was 3.48 years in comparison to 2.86 years for those who ceased MTX within the first year and similar patients reported by others [12, 14]. These recurrences do not reflect resistance to MTX; as CR followed MTX-monotherapy retreatment in eighteen of 26 PCNSL patients who had relapsed. Although MTX-based multi-drug/irradiation therapies (Table 3) are associated with PFS rates ranging from 5.6 months [24] (Cytarabine, Carmustine, etoposide, melphalan with stem cell rescue) to 11 months [25] (Lomustine, procarbazine, Cytarabine and methylprednisolone) to 77.4 months [26] (receiving steroids, cyclophosphamide or etoposide and procarbazine) it is unlikely that these approaches will be the subject of randomized trials in comparison to MTX-monotherapy. The multi-drug therapies [24–37] overall survivals are 60 months [5, 27] 50 months [31] 7 months [26] similar to those we report.

Promising preliminary data suggest efficacy of adding to MTX the drugs Temodar [33] and Rituxan [38]; the provision of autologous stem cell transplantation [39, 40] and low dose brain radiation. These trials are ongoing. Our data provide a benchmark by which to measure the additive value of these approaches. Certainly stem cell transplantation appears a logical addition by which to consolidate the MTX-related CR seen in almost 60% of our MTX recipients. Our early experience with MTX and Temodar and Rituxan points to a reduced interval from diagnosis to CR.

Acknowledgment We would like to thank Alona Muzikansky for her help with statistical studies.

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