

Methotrexate based chemotherapy and deferred radiotherapy for primary central nervous system lymphoma (PCNSL): single institution experience

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Abstract In the following study, we present our experience in the treatment of PCNSL patients using a multi-step schedule combining chemotherapy and deferred radiotherapy. Patients were treated with two modified M-BACOD cycles and then differently according to radiological response. For PR, SD and PD patients, chemotherapy was interrupted and radiotherapy initiated immediately (45 Gy Whole-brain RT). With CR patients, chemotherapy was continued with a combination of HMTX, VCZ, PCB and HD Ara-C up to a total of nine cycles. In 36 patients suitable for evaluation (2 patients had undergone tumour resection): 69.4% (25 of 36) had a complete response (CR), 19.4% (7 of 36) had a partial response (PR), 8.3% (3 of

36) had stable disease (SD), and 2.7% (one of 36) had progressive disease (PD). The PR, SD and PD patients were immediately treated by radiotherapy. In this cohort of patients, we observed 6 CR, 4 PR and 2 PD, respectively, following radiotherapy. At first relapse, a total of 16 CR patients were treated by radiotherapy for a total dose of 45 Gy. The OS was 42.1 months for the entire group of patients. In CR patients treated at the moment of recurrence by salvage radiotherapy, the TTP (time lasting from histological diagnosis until recurrence of disease before RT) was 28.3 months, with a 43.4% of disease free patients observed at 2 years. The median disease-free time observed after complete response to radiotherapy was 10.5 months. In 16 patients (34%), further progression of disease was observed following radiotherapy. Two patients developed extra-CNS disease in the breast and testis. When taking into account the patients with radiotherapy delayed at recurrence, the OS was 48 months and the survival rates were 70% and 60% at 2 years and 5 years, respectively.

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Introduction

Primary CNS lymphoma (PCNSL) is a highly aggressive malignant brain tumour accounting for 1–4% of all intracranial malignancies. In the past, the standard treatment for PCNSL consisted only of whole-brain radiotherapy (WBRT). Although radiotherapy alone was able to induce up to a 70% complete tumour

response, it resulted in a median survival of only 12–18 months and a 5-year survival rate of less than 5% [1]. In the last years, on the basis of reports from several institutions using high-dose methotrexate-based regimen, an increasing number of PCNSL patients were incorporated into schedules combining HD-methotrexate with cranial irradiation. However, to date, no randomized studies comparing radiation alone with radiation plus high-dose MTX-based chemotherapy have been carried out.

A significant argument to this aggressive approach to treatment is the associated late neurotoxicity. Whole-brain radiotherapy and high-dose MTX on their own and more so when combined, expose patients to this unfavourable complication [2]. The risk of neurotoxicity occurs also in younger patients [1, 3] and increases with patient age. In patients older than 60 years of age, virtually all long-term survivors will develop severe delayed neurotoxicity following combined treatment. [4,5]

Several authors have reported significantly better preservation of neurocognitive functions and quality of life in patients treated with chemotherapy alone compared with those who received combined treatment [6].

In the following study, we present our experience in the treatment of PCNSL patients using a multi-step schedule combining chemotherapy and deferred radiotherapy. Patients were treated with two modified M-BACOD cycles and then differently according to radiological response: in Partial responder (PR), Stable disease (SD) and progressive disease (PD) patients, chemotherapy was interrupted and radiotherapy initiated immediately, whereas in CR patients, chemotherapy was continued with a combination of HMTX, VCZ, PCB and HD Ara-C up to a total of nine cycles.

Material and methods

Thirty-eight newly diagnosed immunocompetent patients with PCNSL were included in this study. All patients had histological documentation of PCNSL obtained either by brain biopsy or resection (2). To exclude the inclusion of patients with systemic lymphoma, patients were subjected to a negative staging evaluation, including: chest, abdomen, and pelvic computed tomography scans. A negative human immunodeficiency virus serology and normal blood counts, electrolytes, hepatic and renal functions were also required for inclusion in the study.

In addition, all subjects underwent cranial neuroimaging by magnetic resonance scanning during the

initial stage of the study. Repeat neuroimaging studies (gadolinium-enhanced MRI) were required at completion of the first phase of chemotherapy (2 M-Bacod Cycles) and then every 2 months until disease recurrence. After completion of therapy (CHT+WBRT), all patients were evaluated (gadolinium-enhanced MRI) every 3 months for 2 years, then every 6 months for 3 years and then annually. Lumbar punctures were performed in all patients at admission to the study.

Complete ophthalmologic evaluation, including slit-lamp examination, were performed in all patients at admission to the study, at conclusion of the treatment and then every 6 months. Systemic toxicity was evaluated using the National Cancer Institute common toxicity criteria. Neurotoxicity [7] was evaluated using the Mini-Mental State Examination (MMSE) [8] score and Karnofsky performance status. All patients signed an informed consent.

Chemotherapy treatment

Chemotherapy started on average 1 week (range: 1–3) after diagnosis. Chemotherapy was administered according to a schedule planned in 4 phases (Fig. 1). In the first phase, all patients underwent two M-BACOD cycles (M = Methotrexate 3,500 mg/sqm, B = Bleomycin 4 UI/sqm, C = Cyclophosphamide 600 mg/sqm, O = Vincristine 1 mg/sqm, D = dexamethasone 6 mg/sqm), rescue with leucovorin 10 mg/sqm every 6 h for 6 doses starting 24 h after methotrexate conclusion, and then, according to the radiological response [9], the patients were divided in two arms. All SD, PR and PD patients stopped the chemotherapy and began immediate radiotherapy.

CR patients were treated by a combination of 5 more cycles of MTX based chemotherapy. Each cycle consisted of methotrexate at 3.5 g/sqm infused over 2 h rescue with leucovorin 10 mg/sqm every 6 h for 6 doses starting 24 h after methotrexate conclusion. In addition to methotrexate, procarbazine (100 mg/sqm/day for 7 days) was administered on cycles 1, 3, and 5. At completion of MTX based chemotherapy, the patients received two courses of high-dose cytarabine. Each course consisted of two doses separated by 24 h of cytarabine 3 g/sqm/day infused over 3 h. In this group of patients, radiotherapy was postponed to recurrence.

Radiotherapy

All Patients were treated by whole-brain radiotherapy (WBRT) planned for a total dose of 45 Gy in 1.80-Gy fractions.

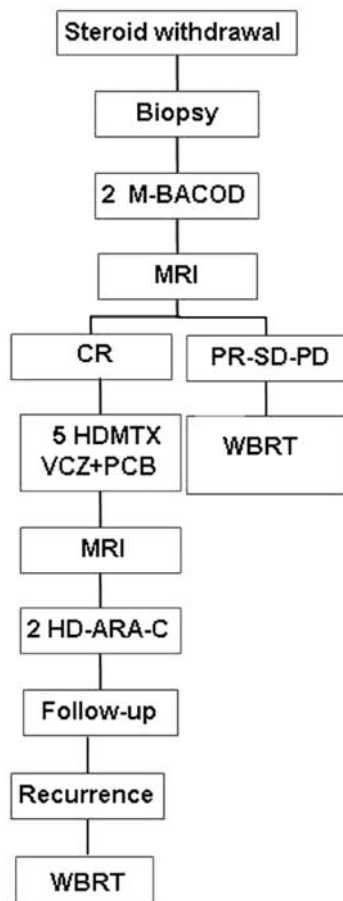


Fig. 1 Schedule of treatment, (CR): Complete responder, (PR): Partial responder, (SD) Stable disease (PD) Progressive Disease patients, M-BACOD: M = Methotrexate, B = Bleomycin, C = Cyclophosphamide, O = Vincristine, D = dexamethasone HDMTX: High dose methotrexate, VCZ: vincristine, PCB: procarbazine HD-AraC: High dose cytosine arabinoside

End points of the study

The primary endpoint was response; secondary endpoints included progression-free survival (PFS), overall survival and changes in mental status.

The response was evaluated according to modified Macdonald’s criteria [9]. Response to treatment was evaluated with brain MRI after two cycles of M-BACOD chemotherapy. A complete response (CR) was defined as resolution of enhancing tumor in patients who were not receiving steroids. A partial response (PR) was defined as a decrease of at least 50% in the tumor size in patients on stable or decreasing doses of steroids. Patients with unequivocal increase in tumor size or appearance of new lesions were classified as having progressive disease (PD); stable disease (SD) represented all other situations. In addition, in the case of patients with CSF or

ocular involvement at diagnosis, complete resolution of disease in these compartments had to be present for classification as CR.

Progression free survival and overall survival were measured from the date of histological diagnosis to the date of the first relapse, death, or last follow-up.

Toxicities were graded according to the common toxicity criteria of the NCI. Survival curves were drawn using the Kaplan Meier product-limit method. All patients who began this treatment regimen were included in the analysis in an intent-to-treat fashion (Table 1).

Results

Thirty-eight patients were enrolled into the trial. Of these, 20 were men and the median age was 56.5 years (Table 1). The median Karnofsky performance status score was 60 and the median MMSE score at baseline was 26.5 with a maximum of 30. Extra-CNS involvement was absent in all patients. No malignant cells were detected in the CSF and no ocular involvement was documented at diagnosis in any of the patients. Gross-total excision was performed in 2 patients and 36 were biopsied.

Table 1 Characteristics of the patients

N°	38
Male	20
Median age (range)	52 years (16–75)
> 70 yrs	3
Median KPS (range)	60 (30–100)
Prior cancer	1
Multiple localisations	15
Single localisation	23
Biopsy	35
Open surgery	3
<i>Histotype (REAL/WHO)</i>	
Diffuse large B-cell Lymph	35
Anaplastic large-cell Ki Lymp	1
Unclassified	2

Table 2 Haematological toxicities after HD-ARAC chemotherapy

	G3	G4
Anemia	28	9
Leukopenia	13	23
Neutropenia	22	61
Thrombocytopenia	15	54
Sepsis	0	1
Bleeding	0	0
Deep Vein Thrombosis	2	

Side effects

During methotrexate based chemotherapy and treatment with procarbazine, no patient developed grade 3 or 4 myelosuppression. Two patients developed transient Grade 3 nephrotoxicity during HDMTX treatment and one patient had an allergic reaction to procarbazine. Other complications included a grade 4 hepatic enzyme elevation and two deep venous thromboses. By contrast, during high dose cytarabine chemotherapy, all patients developed myelosuppression; 22 of 38 patients developed grade 3 (15 patients) or 4 (seven patients) toxicity (Table 2).

A deterioration of neurological function (MMSE, attention deficit, memory impairment, ataxia, and urinary incontinence) in the absence of disease recurrence or other identifiable neurological disease was not observed in any of the patients treated by WBRT at recurrence.

Response

In 36 patients suitable for evaluation (i.e., patients without tumour resection): 69.4% (25 of 36) had a complete response (CR) (Fig. 2), 19.4% (7 of 36) had a partial response (PR), 8.3% (3 of 36) had stable disease (SD), and 2.7% (one of 36) had progressive disease (PD). The PR, SD and PD patients were immediately treated by radiotherapy. In this cohort of patients, we observed 6 CR, 4 PR and 2 PD, respectively, following radiotherapy.

Twenty-five patients finished our complete schedule and nine are presently disease free (13–50 months). As concerns the site of relapse before radiotherapy in CR patients, disease recurred at the original site in 8 patients, at a new site in the brain in 4, at the original and a new site in 2 individuals, in the CSF or in the eyes in 1 case each.

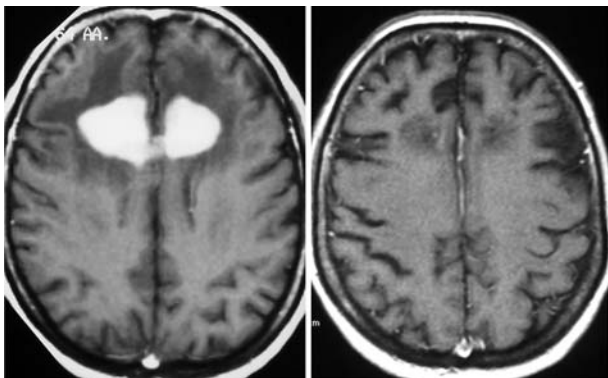


Fig. 2 Complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI after two M-BACOD Cycles

At first relapse, a total of 16 patients with previous CR to chemotherapy were treated by radiotherapy for a total dose of 45 Gy. The OS was 42.1 months for the entire group of patients.

In CR patients treated at the moment of recurrence by salvage radiotherapy, the TTP (time lasting from histological diagnosis and recurrence of disease before WBRT) was 28.3 months, with a 43.4% of disease free patients observed at 2 years. The median time from the end of radiotherapy to further progression of disease was 10.5 months. In 16 patients (34%), further progression of disease was observed following radiotherapy. Two patients developed extra-CNS disease in the breast and testis.

When taking into account the patients with radiotherapy delayed at recurrence, the OS was 48 months and the survival rates were 70% and 60% at 2 years and 5 years, respectively.

Discussion

Unsatisfactory results of radiotherapy (WBRT) alone in the treatment of PCNSLs have led to the use of chemotherapy in combination with WBRT. During the last decade, a large number of phase II studies have shown that addition of high-dose methotrexate (MTX)-based chemotherapy to WBRT, improves survival compared with WBRT alone. Unfortunately, combined treatments have been shown to expose long-term survivors, especially elderly patients, to severe delayed neurotoxicities [10]. Recent studies suggest that treatment with chemotherapy and radiation is associated with significant cognitive impairment and that radiographic abnormalities, such as white matter changes or cortical atrophy, correlate with cognitive function [6, 11]. Therefore, the avoidance of severe long-term neurotoxicity is a major objective among several institutions treating PCNSLs by chemotherapy alone [12–14].

On the other hand, some authors have reported no differences in neurotoxicity rates between PCNSL patients submitted to polychemotherapy alone and patients treated with polychemotherapy followed by WBRT [15]. Unfortunately, no large studies based on prospective neuropsychological testing have been proposed.

HD-MTX chemotherapy followed by WBRT yields a CR rate of 82–88%, a median progression-free survival of 32–40 months, and a median survival of 33 months [16, 17]. CR rate after HD-MTX alone ranges from 30% to 65%, with a median progression-free survival of 13–17 months.

At the moment, when considering these results, the value of WBRT treatment remains indisputable [18, 19] however, the timing of radiotherapy is a matter worthy of discussion. In our opinion, the use of radiotherapy as a systematic consolidation treatment in patients who have achieved a complete remission after chemotherapy is debatable. Some authors have suggested that WBRT consolidation against microscopic residual disease should be preferred to radiotherapy against more bulky disease administered at the time of relapse [20]. Although this is a basic principle of oncology [21], it is unfortunate that the prognosis is still poor for PCNSL patients despite several types of treatments. From the neurologist perspective, a crucial point with respect to treatment is to preserve a good quality of life during the disease free stage in CR patients.

Furthermore, in our opinion it remains disputable whether postponing WBRT at relapse is really detrimental for survival in PCNSL patients. Recently, Nyguen et al. [22] reported the efficacy of whole-brain radiotherapy (WBRT) as salvage therapy for patients who failed initial high-dose methotrexate for PCNSL. In this study, ten patients (37%) achieved a complete radiographic response (CR), and 10 (37%) a partial response to WBRT. Median survival from initiation of WBRT was 10.9 months (range, 0.3–63.7 months). In 2000, Boiardi et al. [23] reported similar results in a small number of recurrent patients after M-BACOD chemotherapy.

In the present study, in a selected group of CR patients after methotrexate based chemotherapy, we postponed radiotherapy at recurrence. In our paper, several points are open to question.

First, in PCNSL therapy, it is unclear whether a combination of several drugs is better than single high dose methotrexate. Some authors suggest that this strategy could carry out as major result only an increase in toxicity [20]. The relatively short progression-free survival reported by several HDMTX based protocols, suggests the addition of other agents to MTX, as happens in systemic disease, may be effective at enhancing the efficacy of chemotherapy. In fact, multi-agent regimens using non-cross-resistant drugs have been essential in achieving a successful treatment of aggressive systemic non-Hodgkin's lymphoma.

Boiardi et al. [24] reported the results of early M-BACOD chemotherapy in a group of 28 PCNSL patients. In this paper, the percentage of CR after two cycles of chemotherapy and prior to WBRT, was 70%. In the former study, the patients were treated immediately after the completion of the M-BACOD chemotherapy by radiotherapy the authors assigned an OS

value of 35 months for the patients CR to M-BACOD. These results are comparable both in terms of response rate and overall survival to the best results available in the literature. Remarkably, the M-BACOD scheme utilized in these studies induced a very low rate of toxic death and an insignificant rate of cognitive dysfunctions in long-term survivors. It could be argued that the M-BACOD scheme chosen for the first step of our protocol represents an unusual combination of agents in the treatment of PCNLs.

In effect, this scheme is mainly constituted of drugs not able to permeate through an intact blood-brain barrier (BBB). Nevertheless, in the early stages of disease, these drugs may reach areas in bulky disease where the integrity of the BBB is disrupted as well documented by enhanced MRI images. For this reason, we used M-BACOD alone during the first and second cycles of chemotherapy, then moving to a HDMTX scheme after the assessment of a complete radiological response by MRI.

On the other hand, in patients with partial response, stable disease or progression, chemotherapy was terminated after the first MRI examination and patients were immediately treated by radiotherapy. In these patients we observed: 6 CR, 4 PR and 2 PD, respectively, after radiotherapy.

As a second step of our schedule, the CR patients were treated by a HDMTX procarbazine, vincristine and HD Ara-C combination. This regimen was derived from a pilot study from the Memorial Sloan-Kettering Cancer Center. In this study, Abrey [25], reported an excellent overall median survival of 60 months using this schedule. These results are 18 months longer than the median survival of 42 months reported by the same group using only methotrexate at the dosage of 1 g/sqm [26].

The main differences between the two schedules were the dose of MTX as well as the addition of procarbazine and vincristine. These results suggest that multiagent therapy and dose intensity of MTX could significantly improve disease control and overall survival.

Basis for choice of treating patients with HD Ara-C. In the patients treated at Istituto Neurologico Besta since 1987, ocular relapse accounts for 15% of all recurrences. It is not established whether a 3,500 mg/sqm dose of methotrexate is adequate to eradicate ocular disease or whether methotrexate penetration is reliable in all patients. Despite the establishment of presumably cytotoxic concentrations of MTX in vitreous and aqueous humour, intraocular lymphoma can persist after 2–3 cycles of high-dose MTX and may relapse after an initial response to i.v. MTX. Adequate ocular

concentrations of cytarabine have been documented after 3 g/sqm [27]. Strauchen [28] reported in six patients with intraocular (vitreous) lymphomas treated with high-dose intravenous cytosine arabinoside (Ara-C), one complete and four partial responses. In the present group of patients, the ocular relapse accounted for 5% (2 patients).

One major limitation of this study is that neuropsychological evaluation was performed in our patients only by MMSE. It is well known that cognitive dysfunctions may be easily missed in the absence of an appropriate psychometric evaluation. However, this limitation is shared by most papers focused on PCNSL treatment [29].

From a general point of view, we are in agreement with Fine [30], who suggests that every new single-arm phase II trial is unlikely to produce significant information in PCNSL lymphoma treatment.

Unfortunately, it is well known that the only phase III study published to date was interrupted after 7 years because of a failure to accrue the necessary number of patients [31]. If we compare the advances obtained in the treatment of GBM patients reported by the EORTC temozolomide based phase III study [32], the situation for PCNLs is completely different. The number of the patients is lower and the treatment requires a series of dedicate structures. This limits the number of centres able to participate in a phase III study and increases the number of phase II studies conducted by pilot centres, with the consequence of a large number of heterogenic treatment schedules.

Only renewed efforts for a multicentric phase III trial comparing deferred radiotherapy to consolidation radiotherapy will hopefully lead to significant improvements in survival and quality of life in these patients [29].

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