High-dose methotrexate combined with procarbazine and CCNU for primary CNS lymphoma in the elderly: results of a prospective pilot and phase II study

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Background: To improve survival of elderly patients with primary central nervous system lymphoma (PCNSL), we conducted a phase II study with high-dose methotrexate (MTX) combined with procarbazine and CCNU. To reduce neurotoxicity, whole-brain irradiation was reserved for patients not responding to chemotherapy.

Patients and methods: High-dose MTX was applied on days 1, 15, and 30, procarbazine on days 1–10, and CCNU on day 1. Study treatment comprised up to three 45-day cycles. There was no lower limit of Karnofsky performance status (KPS).

Results: Thirty patients with PCNSL (n = 29) or primary ocular lymphoma (n = 1) were included (median age 70 years, range 57–79 years). The median initial KPS was 60% (range 30%–90%). Best documented response in 27 assessable patients were 12 of 27 (44.4%) complete remissions, 7 of 27 (25.9%) partial remissions, and 8 of 27 (29.6%) disease progressions. Two patients died of probable treatment-related causes. With a median follow-up of 78 months (range 34–105), the 5-year overall survival is 33%. Eight of 30 patients (26.7%) are currently alive and well, six without signs of leukoencephalopathy.

Conclusion: The combination of high-dose MTX with procarbazine and CCNU is feasible and effective and results in a low rate of leukoencephalopathy. Comorbidity and toxicity remain of concern when treating PCNSL in elderly patients.

Key words: CNS lymphoma, elderly, methotrexate, neurotoxicity, PCNSL

introduction

Primary central nervous system lymphoma (PCNSL) patients have a dismal prognosis despite initial response to steroids and whole-brain radiotherapy (WBRT) [1, 2]. Addition of high-dose methotrexate (MTX) to WBRT has improved the prognosis of patients with PCNSL, resulting in median survival rates of up to 60 months. However, most patients eventually relapse [3–5]. MTX-based, multiagent chemotherapy regimens without WBRT can result in 5-year overall survival (OS) rates of up to 75% [6–10]. Recently, we and others reported that high-dose chemotherapy with autologous stem-cell transplantation (ASCT) and consolidating WBRT showed high remission rates [11, 12]. However, the applicability of intensive regimens is limited to younger patients. As the median age at diagnosis is 60–61 years [13, 14], a substantial proportion of patients with PCNSL cannot be treated within intensive but curative regimens. Surviving patients are at substantial risk of developing leukoencephalopathy with dementia, ataxia, gait disturbances, and incontinence [15]. Particularly those >60 years are prone to this severe neurological complication and, consequently, those who survive have a very poor quality of life. In one study, 100% of patients >60 years who underwent chemoradiotherapy developed clinical neurotoxicity [3]. The main risk factors for leukoencephalopathy are radiotherapy, age >60 years, intrathecal therapy, and chemotherapy after WBRT [3, 15–17]. Taking into account the high risk of neurotoxicity after radiotherapy, we developed an MTX-based treatment protocol combined with oral alkylating agents for patients older than 65 years, omitting intrathecal chemotherapy and restricting WBRT to patients not responding to chemotherapy.

patients and methods

eligibility criteria

Eligible for enrolments were immunocompetent patients with untreated PCNSL or intraocular lymphoma (IOL) >65 years (n = 27) or those below the age of 65 (n = 3) otherwise unfit for our simultaneously initiated high-dose chemotherapy protocol with ASCT [12]. Patients were required to
have a neuropathological diagnosis of PCNSL (n = 29) or IOL (n = 1) on the basis of stereotactic (n = 29) or retinal biopsy (n = 1), respectively. Exclusion criteria were HIV seropositivity, systemic lymphoma manifestation, inadequate bone marrow function (defined as neutrophils <2 × 10^9/L, platelets <100 × 10^9/L), heart or kidney failure, and severe noncompensated pulmonary or liver disease. There was no minimum Karnofsky performance status limit. The study protocol was approved by the participating centres’ local ethics committees. Patients were treated in accordance with the ethical standards of the Helsinki Declaration. This trial was initially conducted as a pilot study and continued as phase II trial. Inclusion and exclusion criteria did not differ between the pilot and study groups. Prior treatment with steroids was allowed and tapered once study treatment had begun.

**staging before study inclusion**

Pretreatment evaluation included contrast-enhanced magnetic resonance imaging (MRI) of the brain. Systemic non-Hodgkin’s lymphoma was ruled out by CT scans of the chest and abdomen and unilateral bone marrow puncture with histologic, cytologic, and immunocytologic examination. Routine laboratory testing, creatinine clearance, echocardiography, and pulmonary function tests were carried out to exclude organ dysfunction as recommended [18]. We only carried out lumbar puncture and examined the cerebrospinal fluid (CSF) and eyes (slit lamp) when we suspected meningeval or ocular involvement.

**study design and treatment protocol**

This trial was carried out as an open-label phase II trial and aimed at including 30 patients. From June 1998 to November 2004, 30 patients were enrolled in the pilot and phase II study from two centers. All patients provided written informed consent.

A chemotherapy cycle of the MCP protocol (Figure 1) consisted of high-dose MTX 3 g/m^2 given i.v. over 4 h at days 1, 15, and 30. Leucovorine rescue (15 mg/m^2 every 6 h) began 24 h after the start of MTX infusion and continued until MTX clearance. Procarbazine 60 mg/m^2 at days 1–10 and CCNU (110 mg/m^2) at day 1 were administered orally. Initial dexamethasone treatment was tapered once methotrexate infusions had begun. Chemotherapy cycles were repeated every 45 days; a maximum of three cycles was planned. WBRT was reserved for patients not responding to chemotherapy. Patients not responding to chemotherapy at any evaluation period were recommended to undergo hyperfractionated WBRT with 50 Gy (2 × 1 Gy/day), which is considered equivalent to conventional irradiation with 20 fractions of 2 Gy, totalling 40 Gy.

**evaluation of response**

Patients were assessed for response after the second application of MTX within the first cycle, before the third cycle, and at the end of therapy. Those with complete or partial responses, or stable disease (SD) with clinical improvement, were allowed to continue on protocol. Patients not responding to therapy (SD without clinical improvement or progressive disease [PD]) were advised to undergo WBRT. During follow-up, we assessed the responses of all patients every 3 months within the first year, every 6 months until year 5, and once annually thereafter. Changes in tumour size were evaluated by MRI of the brain with gadolinium contrast enhancement. Baseline MRI was obtained in all patients before initiating therapy. In the patient with primary IOL, slit lamp examination was required to assess response. For all other patients, remissions were evaluated by MRI with gadolinium contrast according to the The International PCNSL Collaborative Group criteria [18]. Complete remission (CR) was defined as the disappearance of all contrast enhancements in MRI in the absence of corticosteroids. Partial remission (PR) was defined as a ≥50% reduction in tumour size compared with the baseline MRI. PD was defined as ≥25% increase in tumour size or appearance of any new lesion. All other situations were considered as SD. Treatment toxicity was graded according to the Common Toxicity Criteria (CTC, version 3.0).

**results**

**patient characteristics and treatment**

Patient characteristics are summarised in Table 1. Thirty patients (15 females, 15 males) were enrolled from June 1998 to November 2004. Median age at diagnosis was 70 years (range 57–79). Three patients included in this trial, under 65 years (57, 61, and 64 years), did not meet our high-dose protocol’s inclusion criteria [12] due to comorbidity. Twenty-nine patients had measurable, contrast-enhancing MRI lesions; one patient had IOL with no pathologic findings in
Table 1. Patient characteristics

<table>
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<th>Characteristic</th>
<th>No. of patients</th>
<th>%</th>
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<td>50</td>
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<tr>
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<td>3</td>
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<tr>
<td>Initial KPS (%)</td>
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<tr>
<td>Median 30–90</td>
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<td>Prognostic score, MSKCC RPA</td>
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<tr>
<td>Class 1 (KPS 70%)</td>
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<td>43</td>
</tr>
<tr>
<td>Class 2 (KPS &lt;70%)</td>
<td>17</td>
<td>57</td>
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*Three patients, age 57, 61, and 64, were included due to contraindications for more aggressive treatment protocols.

KPS, Karnofsky performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; RPA, recursive partitioning analysis.

MRI. Twelve patients received lumbar puncture; CSF involvement was positive for lymphoma cells in two. Single lesions were detected in 19 patients, 11 had multiple lesions at initial diagnosis. None had evidence of systemic lymphoma at the time of enrolment. According to the recently published prognostic model (MSKCC PCNSL RPA classification) [13], 14 patients fall into classes 2 and 16 into class 3. All histologic specimens were evaluated in an independent pathological review board; histopathologic diagnosis was diffuse large B-cell lymphoma in all cases confirmed by immunoreactivity for CD20 and nuclear BCL6.

All 30 patients received high-dose MTX as initial treatment. The protocol schedule, responses and patient outcomes are depicted in Figure 2.

First cycle. Seventeen patients completed the first cycle and proceeded to the second cycle MCP, and 13 patients did not, due to intracranial thrombocytopenic bleeding (n = 1), hypertension and aortic aneurysm rupture (n = 1), asymptomatic liver toxicity [γ-glutamyltransferase (GGT) elevation grade 3, n = 1; alanine aminotransferase (ALT) elevation grade 3, n = 1], renal insufficiency (grade unknown, n = 1), haematopoietic insufficiency (grade 3, n = 1; grade 4, n = 2), PD (n = 4), and refusal to proceed with therapy (n = 1).

Second cycle. Nine patients completed the second cycle and proceeded to the third cycle; reasons for discontinuing the protocol (n = 8) were creatinine elevation grade 3 (n = 1), acute lethal heart failure (n = 1), enteritis grade 3 (n = 1), haematopoietic insufficiency grade 3 (n = 1), PD (n = 3), and relapse from CR (n = 1).

Response to therapy

Evaluation of response by contrast-enhanced MRI was carried out after two applications of MTX within the first cycle, before the third cycle, and at the end of therapy. Measurable lesions could be detected in 29 of 30 patients; in three patients response could not be evaluated due to unexpected death (n = 2) and immediate proceeding to WBRT (n = 1), respectively. Response data are depicted in detail in Figure 2.

Overall objective response from chemotherapy (PR and CR) was seen in 19 of 27 (70.4%) assessable patients, 12 of 27 (44.4%) patients had a complete response and 7 of 27 (25.9%) achieved a partial response after study treatment.

Follow-up

Eight of 30 (26.7%) patients are alive after a median follow-up of 78 months (range 34–105 months). The median OS and PFS are 15.4 months (95% CI 7.6–65.1) and 5.9 months (95% CI 2.7–26.6), respectively (Figure 3). The intention-to-treat analysis for all 30 patients revealed survival rates of 33.3% (95% CI 16.5–50.2) at both 3 and 5 years. One patient having achieved CR after one cycle MCP died from intracranial bleeding without cerebral lymphoma manifestation after 64 months, possibly as a late complication of therapy. After achieving CR, 5 of 14 patients relapsed after 7, 12, 13, 26, or 65 months. Two patients refused further treatment and three patients received salvage therapy for recurrent PCNSL. Of those, one underwent WBRT alone, one WBRT combined with procarbazine and CCNU; both patients died after 2 and 3 months, respectively. Another patient developed continuous CR after rituximab monotherapy as salvage treatment. When CR was attained from chemotherapy with (n = 2) or without WBRT (n = 12), the median response duration was 63.6 months.

According to the MSKCC PCNSL RPA classification, 13 patients fell into class 2 (intermediate risk, KPS ≥70%) and 17 patients into class 3 (poor prognostic group, KPS <70%). Five-year OS probability of patients in classes 2 and 3 were 38.5% (95% CI 12.0% to 64.9%) and 29.4% (95% CI 7.8% to 51.1%), respectively (Figure 4). Univariate Cox regression analysis for KPS ≥70% showed no significant effect on OS (hazard ratio = 1.3, 95% CI 0.541–3.101, P = 0.56).

Acute toxicity

Toxicity data were available for 28 of 30 patients, with two patients dying early due to PD, thus leading to incomplete data. Chemotherapy was generally well tolerated. Leucopenia and thrombocytopenia were the most frequent toxic effects. Grades 3 and 4 neutropenia, thrombocytopenia, and anaemia were observed in 18 patients (64%), eight patients (29%), and nine patients (32%), respectively. Other Grade 3 toxic effects included transient ALT and GGT elevation without liver dysfunction (2 of 28) and infections during neutropenia (8 of 28). Mild renal dysfunction (grades 1 and 2) was observed in five patients. Two unexpected nonlymphoma-associated, probably treatment-related deaths occurred during the course of study with one patient dying 20 days after initial treatment from thrombocytopenic cerebral haemorrhage, and the second patient died from cardiac failure during therapy. One further
patient died from a ruptured aortic aneurysm which was probably not treatment related.

Of the eight surviving patients, two were irradiated due to intolerance of methotrexate. While we did not assess neurotoxicity via serial neurocognitive function testing, six of eight surviving, nonirradiated patients are in excellent (n = 3, KPS 100), good (n = 2, KPS 90), and moderate (n = 1, KPS 60) general condition; cognitive evaluation revealed no clinical signs of severe leukoencephalopathy (Mini-mental state examination 27, 28, 29, 30, 2 not evaluable). Two long-term surviving patients who required WBRT because of MTX toxicity suffer from dementia and gait disturbances due to progressive leukoencephalopathy—one of them with hemiparesis after ischaemic stroke.

**discussion**

This pilot and phase II study was conducted to assess the efficacy of a high-dose MTX-based chemotherapy protocol in older patients with PCNSL not qualifying for more intensive regimens. All drugs chosen in this protocol can penetrate the intact blood–brain barrier and are commonly used in the treatment of lymphoma. MTX is recognised as the single most effective cytostatic agent in the treatment of PCNSL when doses >1.5 g/m² are applied [3, 4, 8, 19–22]. Compared with other PCNSL treatment regimens [7, 12, 23, 24], our MTX dose...
In one trial with a therapy regimen similar to the one we recently reported [34], on the other hand, two of our patients showed disease control after one and two cycles of 64 and 36+ months, respectively. This observation reflects that a subset of elderly patients has an extremely methotrexate-sensitive PCNSL and are probably unnecessarily overtreated with WBRT alone. This is worrying since a current population-based analysis [35] demonstrates that radiotherapy is the most common treatment modality for older patients with PCNSL. Despite the common perception that high-dose methotrexate is too toxic for older patients, our data show that older patients can tolerate high-dose MTX with acceptable renal toxicity, confirming the observation of others [24, 36].

Clinical signs of leukoencephalopathy after successful PCNSL treatment usually include rapidly progressive dementia, followed by gait disturbances and incontinence [15]. Lymphoma-associated and therapy-associated neurocognitive deficits are frequently indistinguishable, especially in patients presenting with dementia as the initial PCNSL symptom. Furthermore, signs of leukoencephalopathy in MRT (such as white matter lesions) do not necessarily correlate with the degree of clinical deficits. Leukoencephalopathy and treatment-related cognitive impairment are often only distinguishable by the deficits’ chronology. Because patients >60 years are highly vulnerable to treatment-related neurotoxicity with rates of leukoencephalopathy of up to 100% [3] reported, we restricted WBRT to patients not responding to chemotherapy in our trial. Of the eight long-term survivors in our trial, two results fall between the reports of patients older than 60 years and those >70 years.

Our trial’s median OS is relatively short; however, this may well be due to the patients’ low initial median KPS of 60% and their numerous comorbidities. Furthermore, the threshold for stopping chemotherapy in patients who showed moderate side-effects was initially low, and they were taken off study (intention-to-treat). This factor is reflected in the early drop in the survival curve (Figure 3). The 5-year OS of 33% is encouraging, considering our patients’ poor prognostic factors; 17 of 30 included patients (53%) had a KPS <70% at initial diagnosis and fall into class 3 (poor prognostic group) regarding the MSKCC PCNSL RPA classification [13].

Considering our long median follow-up of 78 months, we conclude that ~30% long-term remissions are achievable with MTX-based polychemotherapy and WBRT limited exclusively to nonresponders. Two of 30 patients with PR and intolerance of methotrexate received successful consolidating WBRT leading to ongoing CR for 36+ and 90+ months, both patients suffer from dementia and gait disturbances following WBRT with 36 and 40 Gy. There is still controversy about the significance of consolidating radiotherapy after methotrexate-based chemotherapy. WBRT doses of 40–50 Gy can lead to severe neurotoxicity, particularly in patients >60 years [3]. Promising results for reduced consolidating WBRT of 23.4 Gy were recently reported [34].

MTX monotherapy in patients with PCSNL has lead to 35%–90% remission rates in trials without age restrictions [6, 10, 21, 26–28]. The median PFS rates of trials with [21, 26] and without [6, 27–29] WBRT vary greatly with 32–40 months and 10–17 months, respectively. In contrast, their median OS times have a much narrower range, with 33 months in the two regimens containing WBRT and between 22.8 and 55.4 months in those without WBRT. Assuming that WBRT is the salvage therapy of choice in relapsed elderly patients not having received prior WBRT, these data suggest that the benefit of WBRT in terms of OS does not depend on whether it is administered as first-line or salvage treatment. There is still no generally accepted, standard WBRT dose for this indication.

Few trials have been carried out on the treatment of (exclusively) elderly patients with PCNSL. Subgroup analyses for patients >70 years in those trials that did not exclude older patients are discouraging, with reported median OS rates of 3–7 months with combined modality treatment regimens [30, 31]. In our trial with a therapy regimen similar to the one we present in this paper, MTX 1 g/m² was combined with procarbazine, CCNU, methylprednisolone, and intrathecal therapy with MTX and AraC in patients older than 60 years [32]. The objective response rate (CR and PR) was 48%. After a relatively short median follow-up of 3 years, median survival was 14.3 months. The rate of neurotoxicity was moderate, with a decline in Mini-Mental State Examination scores in three patients and late neurotoxicity in one of 14 long-term responders. Other prospective trials using high-dose MTX-based chemotherapy without WBRT in patients older than 60 years reported median survival rates of 14.3–34 months [4, 7, 22, 32, 33]. Due to our study’s lower 65-year age limit, our
were irradiated because of MTX toxicity, preventing further application of that drug. Both patients have suffered from slowly progressive dementia since WBRT. Of the other surviving patients, five are doing well with practically unimpaired everyday performance status. Considering the poor quality of life in patients suffering from progressive leukoencephalopathy, we suggest that the designation ‘leukoencephalopathy-free survival’ should be discussed as a suitable parameter of outcome for patients with PCNSL.

What can be considered the best treatment regimen for older patients with PCNSL remains controversial. Despite the recommendation to avoid WBRT in older patients aged ≥60 years, the majority of elderly PCNSL patients are offered treatment with WBRT alone, resulting in poor survival rates of 7.6 months [1, 35]. The elderly patient population is relatively understudied and appropriate clinical trials are few and far between. Our experience and that of others [5, 24, 32, 36] demonstrate that high-dose MTX is well tolerated in older patients, provided their renal function is adequate. We maintain that WBRT treatment should be restricted to refractory disease, considering the radiation-vulnerable brains in the elderly and the resulting quality-of-life impairment. The addition of procarbazine and CCNU (as lymphoma-toxic cytostatic agents penetrating the blood–brain barrier) to high-dose MTX may improve remission and survival rates, but the increased haematological toxicity is worrying, demanding great caution when given to older patients.

In conclusion, with its long-term follow-up, our study demonstrates that a proportion of elderly patients with PCNSL can be cured with MTX-based chemotherapy in the absence of obligatory consolidating radiotherapy, leading to a low rate of leukoencephalopathy and consequently high quality of life of surviving patients. A subsequent phase II trial with MCP and additional rituximab in older patients may further increase response rates and OS without compromising treatment tolerability.

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