High-Dose Chemotherapy With Autologous Stem-Cell Transplantation and Hyperfractionated Radiotherapy As First-Line Treatment of Primary CNS Lymphoma

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ABSTRACT

Purpose
To improve survival and reduce toxicity in primary CNS lymphoma (PCNSL) treatment, we conducted a multicenter phase II study with early high-dose chemotherapy (HDT) and autologous stem-cell transplantation (ASCT) followed by hyperfractionated whole-brain radiotherapy (WBRT) for newly diagnosed PCNSL patients younger than 65 years of age.

Patients and Methods
Chemotherapy included three steps: three cycles of methotrexate (8 g/m²); cytarabine (AraC; two doses of 3 g/m²) and thiotepa (40 mg/m²) followed by stem-cell harvest; HDT with carmustine (400 mg/m²) and thiotepa (two doses of 5 mg/kg body weight) followed by ASCT. WBRT (45 Gy, two doses of 1 Gy/d) was administered for consolidation.

Results
Thirty patients with PCNSL younger than 65 years of age (median, 54 years; range, 27 years to 64 years) were enrolled (nine pilot-phase; 21 phase II). Twenty-eight patients responded to methotrexate: six patients with complete remission (CR), 15 patients with partial remission (PR), and seven patients with stable disease (SD) with clinical improvement. Of 26 patients proceeding to AraC and thiotepa, 10 patients achieved CR, 14 patients achieved PR, one patient experienced SD with clinical improvement, and one patient suffered disease progression. Twenty-three patients received HDT plus ASCT, resulting in 15 patients with CRs and eight patients with PRs. After WBRT, 21 of 21 patients had CRs. One patient died from liver failure after methotrexate. HDT was well tolerated apart from WHO grade 3/4 cytopenia. With a median follow-up of 63 months (range, 4 months to 84 months), 5-year overall survival probability is 69% for all patients and 87% for the 23 patients receiving HDT plus ASCT. The 5-year probability of relapse-related death is 21% for all patients (n/H11005 30) and 8.7% for patients treated with HDT plus ASCT (n/H11005 23).

Conclusion
Sequential systemic methotrexate and AraC and thiotepa followed by HDT plus ASCT and hyperfractionated WBRT is very effective with little toxicity as initial therapy for PCNSL.

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INTRODUCTION

Primary CNS lymphoma (PCNSL) accounts for 1% to 2% of all non-Hodgkin’s lymphomas (NHL) and for 2% to 7% of all primary CNS tumors. The incidence has increased dramatically over the past 30 years, particularly in immunocompetent individuals, currently at 0.3 per 100,000 person-years. Prognosis without treatment is comparable with systemic high-grade NHL, and the median survival of untreated patients with PCNSL is approximately 3 months. Steroids and radiotherapy can induce rapid remissions resulting in a median survival of 12 months to 18 months. The use of methotrexate (MTX) -based chemotherapy and whole-brain radiotherapy (WBRT) results in a median survival of 36 months to 60 months. However, recurrent or progressive disease is common, and there is a substantial risk of late neurotoxicity, particularly in patients older than 60 years of age.

High-dose chemotherapy (HDT) and autologous stem-cell transplantation (ASCT) have been established as the most effective treatment for relapsed or refractory systemic NHL resulting in better overall survival (OS) compared with conventional chemotherapy without HDT.

Here, we present a pilot and multicenter phase II trial to evaluate the feasibility and efficacy of HDT...
and ASCT as first-line treatment of patients with PCNSL. The protocol’s rationale was the sequential application of high doses of blood-brain-barrier penetrating water-soluble cytostatics (MTX and cytarabine [AraC]), followed by high-doses of lipophilic alkylating agents (thiotepa, carmustine). Because an increased rate of leukoencephalopathy after intrathecal MTX application as compared with systemic MTX has been reported7 intrathecal chemotherapy was omitted. After chemotherapy, hyperfractionated cranial radiation was administered at two cycles of 1 Gy/d.

PATIENTS AND METHODS

Eligibility Criteria

Immuneocompetent patients age 18 to 65 years with newly diagnosed PCNSL were eligible for enrollment. Patients were required to have a histologic diagnosis of PCNSL by stereotactic biopsy (n = 29) or cytology from CSF (n = 1). Exclusion criteria were: congenital or acquired immunodeficiency, systemic lymphoma manifestation, inadequate bone marrow function (defined as neutrophils < 2 × 10^9/L; platelets < 100 × 10^9/L), heart or kidney failure, severe noncompensated pulmonary or liver disease. The study protocol was approved by the participating centers’ local ethics committees. Nine initially treated pilot patients were included in this analysis. Inclusion and exclusion criteria did not differ between the pilot and study groups. Prior treatment with steroids was allowed.

Staging Before Inclusion in the Study

Pretreatment evaluation included contrast-enhanced magnetic resonance imaging (MRI) of the brain. Systemic NHL was excluded by computed tomography 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 performed to exclude organ dysfunction as recommended.7

Study Design and Treatment Protocol

This trial was performed as an open label, multicenter, phase II trial; 30 patients were planned for inclusion. Between April 1998 and May 1999, nine consecutive patients were enrolled as pilot patients. From July 1999 to May 2003, 21 patients were treated in the phase II study. All patients provided written informed consent. All together, 30 patients from nine centers were treated.

The treatment schedule (Fig 1) consisted of three courses of intravenous MTX 8 g/m^2 given over 4 hours on days 1, 10, and 20. Lecovorine rescue (15 mg/m^2 every 6 hours) began 24 hours after the start of MTX infusion and continued until MTX clearance. Initial dexamethasone treatment was tapered once methotrexate infusions had begun. Patients were assessed for response after the second course of methotrexate, those with complete remission (CR), partial response (PR), or stable disease (SD) with clinical improvement were continued until MTX clearance. Patients not responding to MTX (SD without clinical improvement, or progressive disease [PD]) were treated outside the protocol. For stem-cell mobilization, AraC (3 g/m^3/3 hours) was administered on days 30 and 31 in combination with thiotepa (40 mg/m^2) on day 31. Stem cells were mobilized with subcutaneous recombinant granulocyte colony-stimulating factor (filgrastim, 300 μg/kg body weight [BW] < 75 kg, 480 μg/kg BW ≥ 75 kg) starting on day 35 until collection of peripheral blood progenitor cells (d 40). A minimum of 2 × 10^6 CD34+ cells/kg BW was required. HDT included carmustine 400 mg/m^2 on day 50 and thiotepa 5 mg/kg on days 51 and 52, followed by ASCT on day 56. HDT was supported by recombinant granulocyte colony-stimulating factor from day 61 until WBC was higher than 1 × 10^9/L for 3 days. Standard supportive measures were taken according to institutional guidelines. Hyperfractionated WBRT started on day 90, patients with CR or PR after HDT were radiated with 45 Gy (two cycles of 1 Gy/d) or 50 Gy (two cycles of 1 Gy/d), respectively.

Evaluation of Response

Response to treatment was assessed in all patients before the third application of high-dose MTX, before HDT, on day 30 after transplantation, after WBRT, and approximately every 3 months within the first year, every 6 months until year 5, and once annually in the subsequent years.

Changes in tumor size were evaluated by MRI of the brain with gadolinium. Baseline MRI was obtained in all patients before initiating therapy. In one patient with positive CSF cytology at diagnosis, repeated lumbar puncture was required to assess response. CR was defined as the disappearance of all signal enhancement in MRI. PR was defined as a 50% or more reduction in tumor size compared with the baseline MRI. PD was defined as 25% or more increase in tumor size or appearance of any new lesion.11 All other situations were considered to be SD. In one patient, lymphoma was completely resected initially, this patient was in continuous complete remission during the whole course of the protocol. Treatment toxicity was graded according to WHO criteria.

Statistics

All patients registered (n = 30) were included in the analysis according to the intent-to-treat principle. In addition, we separately analyzed patients having treatment with HDT and ASCT and denoted them as the high-dose population (n = 23).

End points of the study were OS and progression-free survival. OS was defined as time from initial diagnosis until death from any cause. Patients who did not experience the event of interest with respect to OS were considered as censored observations with time from first diagnosis to last follow-up visit as the censoring time. The Kaplan-Meier method was used to estimate survival probabilities with 95% CI. The probability of death due to relapse was estimated using cumulative incidence rates,12 where death due to relapse and death without relapse were considered to be competing risks. Median follow-up was determined for all patients. Calculations were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC).

Results

Patients Characteristics and Treatment

Patient characteristics are summarized in Table 1. Nine patients were treated in the pilot study. Their responses to therapy (nine CRs)
were sufficient to warrant initiation of a multicerter, phase II trial in which 21 patients were included. All together, 30 patients (24 male, six female) were enrolled. Median age was 54 years (range, 27 years to 64 years). Twenty-eight patients had measurable, contrast-enhancing MRI lesions, one patient had primary meningeal involvement without parenchymal tumor, and one patient had no residual disease after a gross total resection of the tumor. Twenty-one patients had single lesions and eight patients had multiple lesions at initial diagnosis. None had evidence of systemic lymphoma at the time of enrollment. The histopathologic diagnosis was large B-cell lymphoma in 29 patients and immunocytoma in one patient.

All 30 patients received MTX as initial treatment. During the pilot phase, four patients received MTX doses less than 8 g/m²: 3.5 g/m² in cycles 1 to 3 (n = 2), 3 g/m² in cycle 1 and 6 g/m² in cycle 2 to 3 (n = 1), 3g/m² in cycle 1 and 8g/m² in cycle 2 to 3 (n = 1). One patient was initially treated with vincristine and procarbazine in addition to MTX, which was considered as a protocol violation. The schedule of the protocol is depicted in Figure 2. After the second cycle of MTX, four patients discontinued the protocol due to refractory disease (n = 1), SD without clinical improvement (n = 1), renal (n = 1) and liver toxicity (n = 1). Twenty-six patients received three cycles of MTX followed by AraC and thiopeta. After AraC and thiopeta, three patients discontinued the protocol due to refractory disease (n = 1), refusal of consent for HDT (n = 1), or poor performance status due to preexisting lung disease (n = 1). The median number of CD34+ cells collected by leukapheresis was 17.99 × 10⁶/kg (range, 2.78 × 10⁶/kg to 52.00 × 10⁶/kg) with a median of one leukapheresis (range, 1 to 2). Eventually, 23 patients were treated with HDT and ASCT. Hyperfractionated WBRT was administered to 21 patients; two patients refused consent for radiation.

**Response to Therapy**

**Response after high-dose MTX.** Twenty eight of 30 patients were assessable for radiographic response during therapy. One patient with exclusively leptomeningeal involvement was monitored by serial CSF samples and meningeal enhancement on MRI. The patient with resected lymphoma had no residual tumor by MRI and was interpreted as continuous CR. After two cycles of MTX, 28 (93%) of 30 patients had SD with clinical improvement or better (6 CRs, 15 PRs, 7 SDs) and were eligible to proceed with the protocol. Two patients showed neither clinical nor radiologic improvement (1 SD, 1 PD) and were therefore removed from the protocol. The course of therapy and response is depicted in Figure 2.

**Response after AraC and thiopeta.** The mobilization therapy with AraC and thiopeta further improved the response rate in the remaining 26 patients; 10 of 26 patients achieved CR and 14 of 26 patients achieved PR before HDT. One patient had SD with continuous clinical improvement and therefore proceeded within the protocol. Another patient showed PD and received radiation off-study. Two additional patients were removed from the protocol due to refusal of consent for HDT (n = 1), or deterioration in pulmonary function (n = 1), both had achieved CR after AraC and thiopeta.

**Response to HDT with ASCT.** Twenty three of 30 patients (77% by intent-to-treat analysis) proceeded to HDT. At day 30 after ASCT, 23 of 23 assessable patients showed either PR (eight patients) or CR (15 patients) in MRI or CSF, respectively. Two patients in CR after HDT and ASCT refused consent for WBRT.

**Response after WBRT.** Twenty-one patients completed the protocol with consolidating WBRT. Subsequently, all patients (21 of 21) had CR by MRI.

**Acute Toxicity**

After high-dose MTX, five (17%) of 30 patients developed a rise in serum-creatinine (two patients grade 1; three patients grade 2). One patient with an initially unknown history of alcohol abuse died due to liver toxicity after the second cycle high-dose MTX. All 23 patients treated with HDT developed grade 4 neutropenia and thrombocytopenia. Median period of neutropenia (WBC, < 1 × 10⁹/L) was 7.5 days (range, 5 days to 11 days). Thrombocytopenia less than 20 × 10⁹/L occurred in 19 of 23 patients with a median duration of 1 day (range, 0 days to 8 days). Neutropenic fever was observed in 12 of 23 patients; one patient developed pulmonary infiltrates interpreted as fungal
pneumonia. After HDT, mucositis with maximum WHO grades 1 or 2 was seen in five patients and one patient, respectively. One patient developed cognitive impairment during WBRT, which resolved spontaneously after completion of radiotherapy. No relevant acute or late lung toxicity (bronchiolitis) was observed. Overall treatment-related mortality (TRM) was 1 of 30 (3%) by intent-to-treat analysis; TRM associated with HDT plus ASCT was 0%.

**Follow-Up and Outcome**

Twenty-three patients completed HDT and ASCT with PR (n = 8) or CR (n = 15), respectively. All of them achieved CR after WBRT; two patients with CR after HDT plus ASCT refused WBRT. Of these 23 patients, three patients (13%) relapsed at 14 months, 15 months, or 67 months after diagnosis, respectively. One patient suffered a relapse within the CNS and the liver.

In summary, seven patients did not undergo HDT: one patient died during MTX therapy, and six patients were excluded from protocol for the following reasons: two patients were in CR after AraC and thiotepa (one patient refused HDT; one patient had low performance status), four patients were sent directly to WBRT due to renal failure after MTX (n = 1) and inadequate remission (n = 3), respectively, resulting in three CRs and one PD. Five of six patients treated off-study with WBRT died during follow-up due to refractory disease (n = 1), relapse 7 to 36 months after diagnosis (n = 3; one systemic, two isolated CNS relapse), and bacterial pneumonia 4 weeks after WBRT (n = 1).

After a median follow-up of 63 months (range, 4 months to 84 months), 20 of 30 patients (66.7%) were alive by intent-to-treat analysis, and 19 (62.6%) of 31 patients who received HDT and ASCT were in sustained CR. The intent-to-treat analysis for all 30 patients revealed stable survival rates of 68.9% (95% CI, 51.9 to 85.9) at both 3 years and 5 years. Estimated survival probability for the 23 patients treated with HDT and ASCT (n = 23) after 3 years and 5 years were both 87.0% (95% CI, 73.2% to 100%; Fig 3). Of note, the 5-year probability of death due to relapse was 21% (95% CI, 10% to 43%) for all patients (n = 30) and 8.7% (95% CI, 2.3% to 32.7%) for patients treated with HDT and ASCT (n = 23; Fig 4). Since relapse was rapidly followed by death, there is almost no difference between the risk of death due to relapse and the risk of relapse.

After a median follow-up of 63 months, five (16.7%) of 30 patients have developed leukoencephalopathy, defined as neurologic deterioration that was not caused by tumor recurrence or any other identifiable cause. Clinically, the patients presented with progressive attention deficits and mnestic impairment and gait disturbances, in addition to diffuse white matter changes in MRI. The doses of carmustine and thiotepa as they are able to penetrate the intact blood-brain-barrier due to their lipophilic properties. Thus, CSF levels in the brain-barrier due to their lipophilic properties. Furthermore, we chose high doses of the alkylating agents carmustine and thiotepa as they are able to penetrate the intact blood-brain-barrier due to their lipophilic properties. Thus, CSF levels in the brain-barrier due to their lipophilic properties. Therefore, the CSF and brain levels in the brain-barrier due to their lipophilic properties. Therefore, the CSF and brain levels in the brain-barrier due to their lipophilic properties. Therefore, the CSF and brain levels...
chemotherapy. All chemotherapeutic agents in our study were used based on their proven efficacy in treating malignant lymphomas.

Over the last decade, numerous clinical trials have demonstrated MTX as the most effective single drug for the treatment of PCNSL. High dose MTX alone13-15 or in combination with WBRT5,7,16-21 achieves response rates of 52% to 100%. Since high leukoencephalopathy rates (26% to 83%) after polychemoradiotherapy have been reported,6,22 several trials have assessed the efficacy of polychemotherapy without radiotherapy. In one such study,23 65 patients were treated with MTX-based polychemotherapy, and a favorable remission rate of 71% was achieved with an overall TRM of 9%.

The results of the trial presented here were analyzed on an intent-to-treat basis. The estimated OS probability of all 30 patients included in the study is equal after 3 years and 5 years, which may imply the curative effect of this combined treatment. These survival rates are comparable with those of patients with systemic high-grade NHL after HDT and ASCT as initial treatment.8 Compared with other dose-intensive, non-HDT trials for PCNSL,6,23 our protocol showed superior remission rates without increased toxicity. Of note, TRM after HDT plus ASCT was 0%. With our long median follow-up of longer than 5 years, the probability of death due to relapse for patients treated with the protocol including HDT plus ASCT is remarkably low at 8.7%.

HDT and ASCT in patients with PCNSL have gained considerable interest over the last few years. This may be due to the fact that (1) a substantial proportion of patients with CR after conventional chemotherapy relapse and cannot be cured by subsequent radiotherapy; (2) there is increasing evidence that combined radiochemotherapy results in high rates of neurotoxicity; (3) the benefit of HDT in high-risk systemic lymphomas has been shown14 and (4) HDT plus ASCT is a well-established and safe procedure resulting in a low rate of complications if performed in specialized hematologic centers.

A recent trial evaluated second-line HDT plus ASCT in 22 patients with refractory or recurrent PCNSL.24 After conditioning with high-dose thiota, busulfan, and cyclophosphamide, survival at 3 years was 63.7%. Several phase II trials including ASCT with25 and without consolidating radiotherapy26,27 as first-line therapy in PCNSL have been published recently. The 3-year OS rates were 55% to 60%.25,26 Toxic deaths related to HDT occurred in up to 18%.27 Busulfan/cyclophosphamide combinations, such as extensively used in transplantation conditioning regimens for systemic lymphoma, may confer a substantial risk of life threatening organ toxicity, especially of the lung and the liver.

We show the feasibility of our protocol for patients with PCNSL as first-line therapy. Patients tolerated induction therapy and HDT with acceptable toxicity. The high survival rates at 5 years suggest that our protocol may be curative in a substantial proportion of patients. To warrant feasibility of HDT and ASCT, only patients age younger than 65 were included. This must be considered when comparing our results with those in the literature because many patients with PCNSL are older than 65 years. Despite hyperfractionation, we still observed late leukoencephalopathy in five of 30 patients. Yet this rate is moderate compared with the literature.5,7 this is of concern. As reported recently by the Radiation Therapy Oncology Group (RTOG 9310), hyperfractionated radiotherapy may delay, but not eliminate, severe neurotoxicity from combined chemoradiotherapy in PCNSL patients.28

It is not yet clear whether patients with CR or PR after HDT benefit from consolidating WBRT. It may thus be advisable to reserve WBRT for refractory or relapsing patients to further reduce the risk of leukoencephalopathy.

In summary, the protocol presented here with HDT plus ASCT combined with hyperfractionated radiotherapy as first-line therapy seems to be able to cure a substantial proportion of patients with moderate toxicity. Subsequent trials are needed to show whether WBRT is required to cure patients with PCNSL.

REFERENCES


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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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