High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system

Thirteen patients (age 38-67 years) with primary lymphoma of the central nervous system (CNS) were treated with methotrexate and cytarabine/thiotepa induction-chemotherapy followed by high-dose carmustine/thiotepa and autologous stem-cell transplantation. Radiotherapy was restricted to patients who did not respond completely to chemotherapy. With a median follow up of 25 months, 3-year DFS and OS was 77%.

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Primary CNS lymphoma (PCNSL) has a very poor prognosis despite responsiveness to steroids and radiotherapy (WBRT).[1,2] Improved outcome with low neurotoxicity was observed after systemic polychemotherapy without WBRT. Nevertheless, WBRT remains essential for curing chemorefractory or relapsing patients.[3] We previously presented a well tolerated and highly effective protocol using HDT and ASCT followed by WBRT for patients <66 years responding to high-dose methotrexate (HD-MTX). Patients who did not respond were referred to salvage WBRT.[4] With a median follow up of 63 months, 5-year overall-survival (OS) was 69%, and the leukoencephalopathy rate 17%. Other studies on HDT and ASCT for first-line treatment showed 3-year OS of up to 57% without and up to 55% with consolidating WBRT.[5-8] Within this pilot phase, we dose-intensified chemotherapy and restricted WBRT to patients who did not respond completely to chemotherapy to limit neurotoxicity. To determine feasibility, the percentage of patients completing the protocol and the grade of acute and late toxicity were evaluated. Patients proceeded to HDT and ASCT irrespective of their response to HD-MTX. According to our earlier ethics committee approved protocol,[4] we conducted this pilot phase for all consecutive patients <70 years until initiating our new phase-II study. Other than the higher age limit, inclusion criteria and pre-treatment evaluation were as previously described.[4] Patients were treated according to the Helsinki Declaration's ethical standards, and all patients provided written informed consent. Treatment schedule included 3 sequential steps: 1) two to four cycles of HD-MTX 8 g/m^2 given over 4 hours at 10-day intervals, leucovorin rescue (15 mg/m^2 every 6 hours) beginning 24 hours after the start of MTX infusion and continued until MTX clearance; 2) two 21-day cycles of cytarabine (1×3 g/m^2 days 1-2) and thiotepa (40 mg/m^2 day 2) followed by filgrastim and stem-cell mobilization after the first cycle (at least 2×10^6 CD34$^+$ cells/kg BW were required); 3) conditioning with carmustine (400 mg/m^2 day 1) and thiotepa (2×5 mg/kgBW days 2-3) followed by ASCT at day 7. Remissions were evaluated by magnetic resonance imaging (MRI) with gadolinium contrast according to the IPCG criteria.[9]

Between February 2003 and June 2006, 13 patients (8 female, 5 male) were treated. Median age was 54 years (range 38-67) and median Karnofsky performance status (KPS) was 90% (range 30-100%). Histopathologic diagnosis was diffuse large-B-cell lymphoma in all cases.

A summary of patient characteristics and treatment outcome is shown in Table 1. Response to MTX was observed in 8 out of 13 patients (61.5%; 3 CR and 5 PR). Thirteen patients underwent 1 cycle AraC/thiotepa, and 5 patients underwent 2 cycles, respectively. Objective response was seen in 61.5% (4 CR, 4 PR). Two patients with symptomatic PD after AraC/thiotepa received WBRT, 1 patient died in PD, the second patient achieved continuous CR. Eleven out of 13 patients proceeded to HDT and ASCT, resulting in 7 CR and 4 PR. Three patients were referred to WBRT after HDT and ASCT due to PR; one patient with PR refused WBRT and died.

During follow-up, one patient died due to systemic relapse after completing therapy in CR.

With a median follow-up of 25 months (range 2-50), 10 out of 13 (77%) patients are alive in excellent mental (n=10) and general condition (n=9). At the most recent follow-up, median Mini-mental State Examination (MMST) was 29/30 (range 26-30), median KPS was 90 (range 70-100). Both three year DFS and OS were 76.9% (Figure 1). Therapy was generally well tolerated, no

Table 1. Patient characteristics and treatment outcome.

Patient	Age/Sex	Initial KPS	IELSG PS	#MTX cycles[¥]	Resp. to MTX	#AraC/TT cycles	Resp. to AraC/TT	Resp. to HDT	WBRT Dose [Gy]	Overall Resp.	Relapse	Survival [mo]	NT	last MMST	last KPS	Cause of death
1	42/W	30	2/5	3	PR	1	PR	CR	n.d.	CR	no	50+	no	30	100	
2	63/M	90	4/5	3	PR	1	PR	PR	36	CR	no	45+	no	29	90	
3	66/W	70	4/4*	4	SD	2	SD	CR	n.d.	CR	no	43+	no	28	90	
4	66/W	90	3/5	4	PD	2	PD	nd	50	CR	no	36+	no[†]	29	70	
5	44/W	90	2/4*	3	PR	2	PD	PR	50	CR	no	25+	no	26	90	
6	54/W	90	3/5	2	SD	1	PD	nd	4	PD	PD	2	no	--	--	PCNSL
7	58/M	90	1/4*	4	CR	2	CR	CR	n.d.	CR	yes	11	no	--	--	lymphoma[‡]
8	39/M	80	1/5	3	PR	2	PR	CR	n.d.	CR	no	24+	no	27	90	
9	67/W	90	2/4*	2	PD	1	PD	PR	n.d.	PR	PD	3	no	--	--	PCNSL
10	38/W	90	1/4*	4	CR	2	CR	CR	n.d.	CR	no	22+	no	30	100	
11	61/M	70	3/4*	1	SD	2	CR	CR	n.d.	CR	no	17+	no	30	100	
12	53/M	90	1/4*	3	CR	2	CR	CR	n.d.	CR	no	15+	no	29	90	
13	46/W	100	2/4*	4	PR	1	PR	PR	45	CR	no	11+	no	30	100	
Median	54	90										25		29	90	

KPS: Karnofsky performance status; IELSG PS: International Extranodal Lymphoma Study Group Prognostic Score[10]; Resp.: Response; MTX: methotrexate; Ara C: cytarabine; TT: thiotepa; HDT: high-dose chemotherapy; Gy: Gray; mo: months; NT: neurotoxicity; MMST: Mini Mental State Examination; nd: not done. [¥]Reasons for discontinuing MTX were transient creatinine elevation (n=3) or progressive lymphoma (n=2). [†]Patient 4 suffers from gait disturbances after a stroke. [‡]Patient 7 died after systemic and brain relapse of NHL.

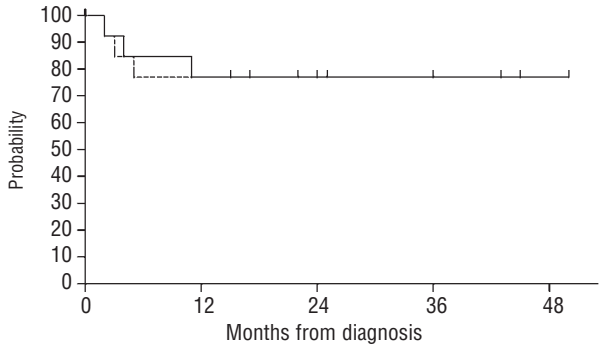

Figure 1. Kaplan-Meier plot: disease-free survival (- -) and overall survival (–) from time of initial diagnosis of all patients.

patient died of treatment-related causes. In our previous trial,[4] 5-year OS of all patients was 69% and 87% of those treated with HDT and ASCT. However, the reported rate of severe leukoencephalopathy (24%) in irradiated patients led us to restrict WBRT to patients not in CR after finishing chemotherapy. Our previous protocol[4] had shown excellent tolerability. Therefore, we increased the number of chemotherapy cycles and escalated the thiotepa-dose within the conditioning regimen in this pilot phase. In contrast to the earlier study, all patients were supposed to proceed to HDT and ASCT irrespective of their response to HDMTX. Despite these modifications, OS in this study is similar to our trial with obligatory WBRT[4] and we have not so far observed severe neurotoxicity.

Taken together, the results of this pilot phase are promising and support our hypothesis that WBRT may not be necessary to cure many of the patients in CR after HDT and ASCT, as long as adequate doses of chemotherapy are applied. The moderate acute toxicity and lack of severe neurotoxicity confirm the feasibility of this high-dose protocol. A prospective multicenter phase-II trial using this treatment regimen has been initiated.

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Redundant publications: parts of our preliminary results were presented at the ASH-Conference 2006 and EBMT 2007. We have also disclosed previous presentations, reports or publications containing any material appearing in this article.

Key words: PCNSL, high-dose chemotherapy, stem-cell transplantation, whole-brain-radiotherapy, neurotoxicity

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