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ORIGINAL ARTICLE

High-dose chemotherapy with autologous stem cell transplantation as first-line therapy for primary CNS lymphoma in patients younger than 60 years: a multicenter phase II study of the GOELAMS group

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The optimum treatment of primary CNS lymphoma (PCNSL) is not yet determined. The objective of this study was to assess the safety and efficacy of initial methotrexate-based chemotherapy followed by high-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) in patients with newly diagnosed PCNSL. Twenty-five patients received two courses of initial chemotherapy combining methotrexate, etoposide, carmustine and methylprednisolone, and one course of ifosfamide–cytarabine followed by peripheral stem cell collection. Seventeen responsive patients then received HDT using carmustine, etoposide, cytarabine and melphalan with autologous stem cell rescue. After ASCT for responding patients or after salvage therapy for non-responders, whole brain radiation therapy at a dose of 30 Gy was delivered. The objective response rate to the induction chemotherapy was 84%. Four of the 21 responding patients did not have ASCT because of toxicity or refusal. With a median follow-up time of 34 months, the projected event free survival rate is 46% at 4 years. Projected overall survival is 64% at 4 years. Sixteen patients are actually in continuous complete response. No evidence of late treatment-related toxicity was observed. This treatment approach appears feasible in newly diagnosed PCNSL with encouraging results.
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Introduction

The combination of high-dose methotrexate (HD-MTX) (MTX > 1.5 g/m^2) and cranial radiotherapy (RT) represents the actual standard treatment of primary CNS lymphoma (PCNSL). In patients younger than 60 years, a median survival of 4 years can be observed after this therapeutic approach.[1,2] Unfortunately, the combination of chemotherapy and RT leads to delayed neurotoxicity, mainly in older patients. Encouraging results have been published recently with chemotherapy alone in patients older than 60 years.[3] A possibility of decreasing or suppressing the RT is to increase the efficacy of the initial chemotherapy. Encouraging results have been published with high-dose chemotherapy and autologous stem cell transplantation (ASCT) in the treatment of relapsed patients.[4,5] This report presents the results of a prospective multicenter trial evaluating the role of high-dose therapy with ASCT followed by RT as first-line treatment of PCNSL in 25 patients.

Patients and methods

Patients were eligible for the study if they had a newly (<3months) diagnosed pure PCNSL, histologically confirmed by brain biopsy or CSF cytology, if they were HIV negative, if age was ⩽60 years and if informed consent was signed. Only diffuse large B-cell lymphomas were included. All cases underwent a pathological central review. Staging evaluation included a complete history and physical examination, a computed tomographic (CT) scan of the brain, a lumbar puncture with CSF cytology, glucose and protein assays, and a thoraco-abdominal CT scan. All patients received the same initial chemotherapy regimen (MVBP) consisting of two courses of high-dose methotrexate, 3 g/m^2, on days 1 and 15 with leucovorin rescue. Carmustine (100 mg/m^2) on day 3; etoposide 100 mg/m^2 on day 2 and methylprednisolone 60 mg/m^2 on days 1–5. The interval between two courses of MVBP was 21 days.

Clinical evaluation and CT scanning were performed after the second cycle of MVBP. If a complete response (CR) or partial response (PR) was obtained, a chemotherapy regimen associating ifosfamide 1500 mg/m^2 on days 1–3 and cytarabine 1000 mg/m^2 twice daily on days 1 and 2 was administered for mobilization of peripheral blood stem cells, in combination with G-CSF. If patients failed (stable disease or progressive disease), two courses of salvage therapy conditioning etoposide (150 mg/m^2 on days 1 and 2) and cytarabine (1000 mg/m^2 per 12 h on days 1 and 2) were administered before RT. All patients received intrathecal chemotherapy with six intrathecal treatments with methotrexate 20 mg, cytarabine 50 mg and methylprednisolone 40 mg. Conditioning for the ASCT was BEAM (BCNU 300 mg/m^2 on day 1, VP16, 200 mg/m^2/day on days 2–5 (total dose 800 mg/m^2), cytarabine 100 mg/m^2 twice daily on days 2–5 (total dose 800 mg/m^2) and melphalan 140 mg/m^2 on day 6). After ASCT, all patients received G-CSF. RT was delivered in patients who initially responded, or after salvage therapy for non-responders. The whole brain (with lower limit at C_2–C_3) was irradiated to 30 Gy in 17 fractions of 1.8 Gy. A 10 Gy boost was administered in cases with residual tumor on a CT scan performed after ASCT or after the last course of chemotherapy before RT.

During the follow-up period, CT scans were performed every 6 months for 2 years and every 12 months over the next 3 years.

The primary treatment endpoint was overall survival (OS). The secondary endpoints were response rate, event-free survival (EFS), feasibility and the treatment safety.

Results

Twenty-five patients from 11 centers were included in this trial between July 1999 and November 2001. Patient characteristics are summarized in Table 1. Sixteen women and nine men were included with a median age of 51 years (range 21–60).

Acute toxicity of MVBP

During the first two courses of MVBP, myelosuppression was acceptable: no grade 3–4 thrombocytopenia was observed; seven patients experienced a polymorphonuclear cell number of less than 0.5 G/l. One case of cerebral aspergillosis, which resolved with antifungal drugs, and two non-hematological toxicities linked to methotrexate therapy were observed: a grade 2 interstitial pneumonitis and a grade 2 renal toxicity (spontaneous resolution).

ASCT

The median number of CD34+ cells infused was 31.7×10^6 cells/kg (range: 1.84–145.5). The median time to engraftment was 8 days for neutrophil recovery >0.5 G/l (range 6–15) and 2 days for platelet recovery >20 G/l (range 0–8).

Two major toxicities occurred: one lethal septic shock during conditioning therapy and one grade 4 neurological toxicity with epilepsy and coma.

Table 1 Patients characteristics

Patients characteristics	*No.*
Number	25
Age (years)	
Median	51
Range	(21–60)
Sex	
Men	9
Women	16
Pathology	
Diffuse large cell	25
ECOG performance status	
0	3
1	10
2	4
3	6
4	2
Symptoms at diagnosis	
Paralysis or weakness	11
Sensory abnormalities	8
Cognitive abnormalities	11
Number of tumors	
1	10
2	6
>3	9
LDH level	
Normal	20
Increased	5
Positive CNS fluid	1
Prognostic score[10]	
Low	11
Intermediate	12
High	2

Abbreviations: CNS = central nervous system; LDH = lactate dehydrogenase.

Response to therapy and survival

Response to initial therapy was assessable in all patients. Twenty-one (11 CR and 10 PR) out of the 25 patients responsed to the two courses of MVBP. One of the four patients with primary refractory disease received ASCT after salvage treatment and is still in complete remission. Only 17 patients received ASCT because of two refusals and two extrahematological toxicities (invasive aspergillosis and renal toxicity). After ASCT, 16 patients were evaluable as one toxic death occurred. Thirteen patients were in CR. Six patients in PR after conventional chemotherapy were in CR after ASCT. All patients except one received RT; the three patients in PR after ASCT received a 10 Gy boost. Two other patients entered CR after RT after ASCT. The four patients, who were not grafted owing to toxicity or refusal, were irradiated and achieved CR at the end of the treatment.

With a median follow-up of 34 months (range 2–52), five out of the 20 patients (25%) in CR after completion of treatment have relapsed (one multifocal and four local relapses), two out of the four non-grafted and three out of the 17 grafted patients. Currently, the median time for OS

has not been reached. Projected survival rate at 4 years is 64% (see Figure 1): eight deaths occured, four because of initial progression, one from toxicity during ASCT and three of relapse.

Median EFS time is 40 months with a projected EFS rate of 46% at 4 years (see Figure 2). For the 17 grafted patients, the EFS and DFS rates at 3 years are 66 and 75%, respectively.

Sixteen patients are currently in complete remission and evaluable for late neurotoxicity. Two patients have developed neurological sequelae, memory dysfunction and equilibrium dysbalance, directly linked to the initial disease in one case. At this time, no signs of leucoencephalopathy have been seen on CT but the median follow-up is still short.

Discussion

High-dose methotrexate ($>1\,g/m^2$) and WBRT is the current standard treatment for PCNSL in the immunocompetent population, especially in younger patients.[1,2] However, late neurotoxicity is a major problem with this combination, occurring in about 30–80% of patients older than 60 years.[1,6,7] It is related to age as well as schedule and dose of RT. A recent publication showed encouraging results with chemotherapy alone combining high-dose methotrexate, lomustine, procarbazine and methylprednisone in patients older than 60 years with an overall median survival time of 14.3 months.[3] Conversely, reduction in the RT dose from 45 to 30.6 Gy in patients younger than 60 years in CR may result in an increased risk of relapse and lower OS,[6] suggesting that the association of chemotherapy and RT remains standard treatment for PCNSL in young patients.

Encouraging results have been published with high-dose chemotherapy with ASCT in relapsing patients.[4,5] Only two publications report ASCT as first-line therapy without RT. The first study showed disappointing results, probably because of the lack of RT, with an objective response rate to the induction-phase chemotherapy of 57% in 28 patients and an overall median evert-free survival time of 5.6 months.[8] The second study[9] reported seven patients treated with HD-MTX-based induction chemotherapy followed by thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain RT: results were encouraging, with five patients in CR at the time of publication but the number of patients was small and follow-up was short. Our study shows that this therapeutic approach is feasible, as 17 out of the 21 patients eligible for ASCT were grafted and only one toxic death was observed. However, with a median follow-up of 34 months, the EFS and OS rates appear comparable to those seen with the combination of HD-MDX and RT in the same age group of patients.

We therefore suggest that ASCT should be considered only for patients with primary refractory disease, in relapse or in PR after conventional chemotherapy. The role and the dose of RT as part of initial therapy in young patients remains to be determined and a multicentric randomized trial is required.

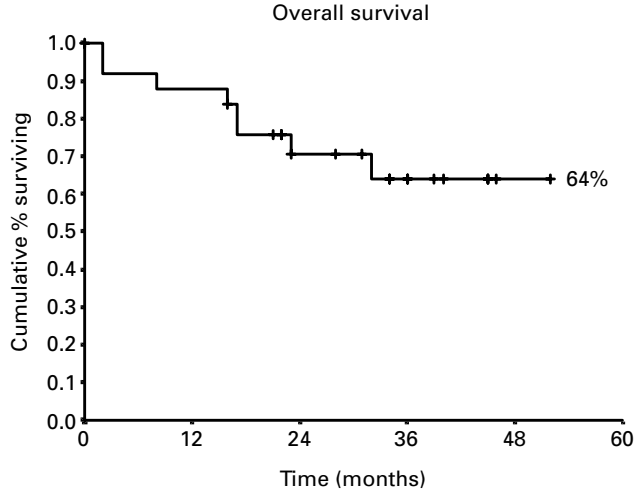

Figure 1 Kaplan–Meier OS of the entire group.

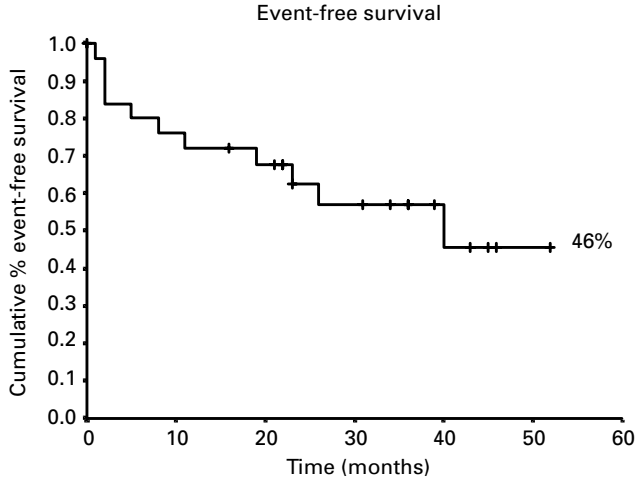

Figure 2 Kaplan–Meier EFS of the entire group.

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