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First-line autologous stem cell transplantation in primary CNS lymphoma

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Abstract: The treatment of primary central nervous system lymphoma (PCNSL) has been considerably improved over recent years. In this article, we report six cases of PCNSL treated by first-line induction chemotherapy followed by intensive chemotherapy and autologous stem cell transplantation (ASCT). Six immunocompetent patients presenting with a PCNSL, confirmed by thoraco-abdomino-pelvic computer tomography scan and bone marrow biopsy, were treated with induction chemotherapy followed by BEAM intensive chemotherapy and ASCT and radiotherapy. At the end of the treatment, all the patients were in complete remission. After a median follow-up of 41.5 months (17–70 months), four patients were alive without signs of relapse (median survival: 35.5 months). Two patients died from relapse at 19 and 23 months. The neurotoxicity was low with epilepsy in one patient and persistent left side dysesthesia in another one. These results are fairly encouraging. Other studies with greater numbers of patients and longer follow-up are needed to confirm this study.

M. Brevet, R. Garidi, B. Gruson, B. Royer, I. Vaida, G. Damaj

Centre Hospitalier Universitaire Amiens, Service des Maladies du Sang, Rue Laennec, France

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Correspondence: Dr. G. Damaj, Centre Hospitalier Universitaire Amiens, Service des Maladies du Sang. Rue Laennec, 80054, Amiens Cedex 01, France
Tel: +33-3-22455915
Fax: +33-3-22455797
e-mail: damaj.gandhi@chu-amiens.fr

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The incidence of primary central nervous system lymphoma (PCNSL) in immunocompetent subjects is increasing. PCNSL in immunocompetent subjects constitutes a distinct form of non-Hodgkin's lymphoma (NHL). They represent 5–10% of all localized NHLs and 4% of all brain tumors. The pathophysiology of PCNSL remains enigmatic, but their incidence, like that of systemic NHL, is on the increase. Histologically, PCNSL usually corresponds to a large diffuse B-cell lymphoma or Burkitt's lymphoma, while T-cell lymphomas are rare. The treatment of PCNSL has been considerably improved over recent years. For a long time, PCNSL were treated by exclusive radiotherapy, but a combination of chemotherapy followed by consolidation radiotherapy is now the most widely used treatment regimen. Relapse and treatment-induced neurotoxicity remain the two main problems. Intensive chemotherapy followed by autologous stem cell transplantation (ASCT) for the treatment of PCNSL was reported for the first time in 1996 (1). Two other recent studies (2, 3) have demonstrated its feasibility in patients with PCNSL, either as treatment for relapse or as first-line therapy. In this article, we report six cases of PCNSL treated by first-line induction chemotherapy followed by intensive chemotherapy and ASCT.

Patients and methods

Patients

Between April 1998 and September 2002, six consecutive patients with the diagnosis of PCNSL received first line intensive chemotherapy. CNS lesions were documented by computer tomography (CT) scan and magnetic resonance imagery. The histological diagnosis was based on stereotaxic brain biopsy. Thoraco-abdomino-pelvic CT-scan, bone marrow biopsy, lumbar puncture with cytological study, slit-lamp examination, serum LDH and HIV serology were performed in all patients at the time of diagnosis.

Treatment

Two courses of MBVP [methotrexate, 3 g/m^2 on D1 and D15, i.v. (total dose 6 g/m^2) with calcium folinate rescue starting at D2; carmustine, 100 mg/m^2 on D3, i.v. (total dose 100 mg/m^2); etoposide, 100 mg/m^2 on D2 (total dose 100 mg/m^2), i.v.;

methylprednisolone, 60 mg/m^2 from D1 to D5, i.v. (total dose 300 mg/m^2)] were administered at 1-month interval. Intrathecal chemotherapy (cytarabine 50 mg, methotrexate 18 mg and methylprednisolone 40 mg) was administered on D1 and D15 of each course.

Peripheral stem cells were collected after a course of ifosfamide (1500 mg/m^2 from D1 to D3, i.v. (total dose 4500 mg/m^2) and cytarabine 2 g/m^2 D1 and D2, i.v. (total dose 4 g/m^2) and were mobilized by granulocyte growth factor administered by subcutaneous injection from D5 at the dose of 5 g/kg/d. A fifth dose of intrathecal chemotherapy was administered on D1 of this course.

BEAM conditioning [carmustine, 300 mg/m^2 on D1, i.v. (total dose 300 mg/m^2); cytarabine, 200 mg/m^2 from D2 to D5, i.v. (total dose 800 mg/m^2); etoposide, 400 mg/m^2 from D2 to D5, i.v. (total dose 1600 mg/m^2); melphalan, 140 mg/m^2 D6, i.v. (total dose 140 mg/m^2); methylprednisolone, 60 mg from D1 to D6, i.v. (total dose 360 mg)] followed by ASCT was administered 4–6 wk after the last course of chemotherapy. Granulocyte growth factors were administered from D4 and until a polymorphonuclear neutrophil count greater than 0.5/l (500 per mm^3) was obtained.

Radiotherapy was administered, for a maximum of 8 wk after ASCT, at a dose of 30 Gy in 16 doses if complete remission (CR), or at a dose 30 Gy + 10 Gy to the tumor bed in the case of PR (Table 1).

The response to treatment was evaluated after two courses of MBVP and then after ASCT and radiotherapy.

Table 1. Treatment protocol

2 x MBVP
D1 and D15: Methotrexate 600 mg/m^2 by 30-minute infusion and 2400 mg/m^2 by infusion over 23 h 30 min, i.v.
D2: Etoposide 100 mg/m^2, i.v.
D2: BCNU 100 mg/m^2, i.v.
D1 to D5 Methylprednisolone 20 mg/m^2/8 h, i.v.
Intrathecal chemotherapy* on D1 and D15 of the 2 courses of MBVP

Brain CT

If PR > 50% or CR

D1-D3: Ifosfamide 1500 mg/m^2, i.v.
Mesna 800 mg DT/8 h, i.v.
D1-D2: Cytarabine 1 g/m^2/12 h, i.v.
Filgrastim (5 µg/kg/day) from D5 until evening before last dose of cytarabine, subcutaneous

Intrathecal chemotherapy on D1*

PSC collection

BEAM + autologous SCT

D-7: BCNU 300 mg/m^2
D-6 to D-3: Cytarabine 100 mg/m^2/12 h, i.v.
D-6 to D-3: Etoposide 200 mg/m^2/12 h, i.v.
D-2: Melphalan 140 mg/m^2, i.v.
D0: Reinjection of PSC
Filgrastim from D4 until neutrophils > 500/mm^3 for 3 days, subcutaneous

Radiotherapy:

Maximum of 8 wk after autologous SCT
If CR: 30 Gy to whole brain
If PR: 30 Gy to whole brain and 10 Gy to tumour bed

if PR < 50%

Two cycles of:
D1-D2: Etoposide 150 mg/m^2, i.v.
D1-D2: Cytarabine 1 g/m^2/12 h, i.v.

Radiotherapy
30 Gy to whole brain
10 Gy to tumour bed

Intrathecal chemotherapy on D1* (first cycle)

MBVP, methotrexate, etoposide, carmustine, methylprednisolone; PR, partial remission; CR, complete remission; SCT, stem cell transplantation.
*Intrathecal chemotherapy: except intracranial hypertension, five lumbar punctures, 18 mg of methotrexate, 50 mg of cytarabine, 40 mg of methylprednisolone.

Follow-up and assessment

Evaluation during the study and the follow-up period included: a clinical evaluation, performance status (PS), cranial CT and MRI without and with contrast, ophthalmologic examination with slit lamp and CSF examination obtained at the time of administration of each intrathecal chemotherapy. These evaluations were performed every 4 wk (before each cycle of chemotherapy), during the follow-up period, every 3 months thereafter until progression. Response to treatment was based on the following criteria: CR referred to the absence of any contrast enhancement on the CT or MRI of the brain. PR referred to at least a 50% reduction in the product of the perpendicular diameters of the contrast-enhanced area with no new lesion. PD referred to an increase of 25% or more in the product of the contrast-enhanced area or the appearance of new lesions in the CNS, eye, or leptomeningeal space. Stable disease corresponded to all other situations.

Results

Six patients (four males and two females) were treated according to this regimen. The median age was 53 yr (range: 30–66 yr). All patients were HIV negative. The pathologic diagnoses were diffuse large B-cell lymphoma for all cases. The primary nature of CNS lymphoma was confirmed by thoraco-abdomino-pelvic CT scan and negative bone marrow biopsy. PET scan was not available. None of these patients had been previously treated for systemic NHL, CNS lymphoma or brain tumor. At diagnosis, three of the six patients had a PS of 3, two had a PS of 0 and one had a PS of 1. All patients had a leukocyte count greater than 4 G/L and a platelet count greater than 150 G/L. Serum LDH levels were greater than the upper limit of normal in three cases.

One patient received an interim course (cytarabine 2 g/m^2 for 2 d) between stem cell collection and ASCT. Two patients received only three injections of methotrexate due to the development of acute renal failure. Intrathecal chemotherapy

Table 2. Patient characteristics

Gender/age	Site	Chemotherapy	Radiotherapy	ASCT	Response	Duration first CR	Relapse	State	Neurotoxicity
M/44	PCNSL	2 MBVP + 3 IT Holo/Ara Ara 2 g/m^2 D1, D2	30 Gy	BEAM	CR	18 months	PCNSL	Dead	None
M/58	PCNSL/CSF	2 MBVP + 5 IT Holo/Ara	/	BEAM	CR	12 months	/	Alive	None
M/48	PCNSL	3 MBVP Holo/Ara	30 Gy	BEAM	CR	22 months	PCNSL	Dead	None
F/66	PCNSL	2 MBVP Holo/Ara	/	BEAM	CR	33 months	/	Alive	None
M/59	PCNSL	2 MBVP + 5 IT Holo/Ara	20 Gy	BEAM	CR	22 months	/	Alive	None
F/30	PCNSL	2 MBVP + 3 IT Holo/Ara	30 Gy	BEAM	CR	63 months	/	Alive	None

Ara, cytarabine; ASCT, autologous stem cell transplantation; BEAM, Carmustine, Etoposide, Adriamycin, Melphalan; Holo, ifosfamide; IT, intrathecal; CSF, cerebrospinal fluid; MBVP, methotrexate, etoposide, carmustine, Methylprednisolone; CR, complete remission; PCNSL, primary central nervous system lymphoma.

was administered in four patients. In the others, lumbar puncture was impossible for technical reasons. The lymphoma was usually multifocal (4/6), involving the cerebellum in three patients. The cerebrospinal fluid (CSF) was invaded in only one case. None of the patients presented intraocular tumor. All patients received the complete course of treatment except for two patients who did not receive the final radiotherapy.

Two patients achieved CR after induction chemotherapy, four obtained PR (two with PR > 75%). All patients were in CR at the end of treatment.

Two patients relapsed 19 and 23 months after remission. The first one died before starting salvage therapy; the second one received a salvage chemotherapy followed by second BEAM intensification and ASCT. Second complete remission was obtained. The patient died 64 months after the diagnosis from a second relapse (Table 2).

After a median follow-up of 41.5 months (range: 17–70 months), four patients were still alive without lymphoma, 17, 31, 40, and 70 months after the diagnosis (median survival: 35.5 months) (CR = 4).

Toxicity

All patients suffered from grade 4 neutropenia with severe infectious complications documented in two patients. One patient was readmitted with septic shock secondary to *Escherichia coli* septicemia; the second had methicillin-resistant aureus staphyloccus colitis. Reversible grade 2 renal failure after the second cycle of chemotherapy was documented in two patients (and did not receive methotrexate at day 15).

Neurotoxicity

Clinical neurological examinations performed during treatment showed improvement of cognitive functions concomitant with the response to treatment. One patient suffered from algoneurodystrophy of the left superior limb which disappeared by the fourth month after the end of therapy. Two patients suffered from neurological sequelae. One patient developed epilepsy that is well controlled by antiepileptic treatment, and the other suffered from permanent dysesthesia of the left hemi corpus.

Discussion

For a long time, radiotherapy was the 'gold standard' for the treatment of PCNSL, with an objective response rate of 90–95%. Unfortunately, patients relapsed in the short term resulting in a median survival of 14–18 months and a 3-year survival rate of 20% (4). Chemotherapy alone (high-dose methotrexate alone or in combination with other agents) may avoid the neurotoxicity of the chemo-radiotherapy combination, but the median survival remains low (5). The median survival rate after a combination of chemotherapy and radiotherapy is between 37% and 60% (6–8). Salvage chemotherapy achieves a second CR in less than one half of cases and the median survival of patients after relapse ranges from 2 to 14 months. Neurotoxicity is a major problem especially after combined therapy with an encephalopathy incidence of between 26% at 5 yr (9) and virtually 100% in long-term survival patients (10). Table 3 summarizes the results of several studies using chemotherapy alone or a combination of chemotherapy and radiotherapy.

According to several recently published studies, ASCT appears to be not only well tolerated, but also an effective treatment modality for patients, whether administered, as first-line treatment or after relapse. In previous studies, patients were treated with intensive chemotherapy followed by ASCT without radiotherapy. In a series of 20 patients receiving second-line ASCT, Soussain *et al.* (3) reported, in a series of 22 refractory or relapsed patients, treated by intensive chemotherapy (thiotepa, busulfan, and cyclophosphamide) followed by haematopoietic stem cell rescue, an 80% CR rate with 63.7% 3-year survival rate, and three relapses at 3, 5, and 60 months. In a series of 28 patients with *de novo* PCNSL treated by methotrexate and

Table 3. Review of the literature

References	*n*	Treatment	Radiotherapy	Results	Comments
2	28	MTX, Ara-c BEAM	–	EFS 14 months for transplanted patients*	Fourteen patients received BEAM Median FU = 28 months No treatment-related neurotoxicity
3	22	CYVE IC + HCR	–	CR = 80%* 3 yr OS = 60%* 3 yr EFS = 53%*	Twenty patients received IC + HCR Median FU = 41.5 months Neurological toxicity: 07 patients
6	25	MTX 3.5 g/m^2	+	88% response rate, median survival: 33 months	59% relapse rate
7	52	MPV Ara-C	±	Median survival: 60 months	Twenty-two patients did not receive radiotherapy
11	10	DHAP	±	70% response rate, 40% of long-term remissions	Four new diagnoses, six relapses, some of whom were not treated by radiotherapy
12	10	PCV	+	100% response rate, median survival: 30 months	PCV after radiotherapy, one patient received carmustine
13	13	MTX 3.5 g/m^2	+	92% response rate, median survival: 9 months	Survival > 54 months
14	74	MTX	–	65% complete response rate, median survival: 40.7 months	
15	31	MTX 1 g/m^2	+	64% response rate, median survival: 41 months	
16	14	MTV IT Ara-C	–	100% response rate, median PFS: 16.5 months	68.8% of patients alive at 54 months two patients: severe leukoencephalopathy
17	19	BOMES	+	84% response rate, median PFS: 6 months	Five patients: concomitant systemic lymphoma
18	19	MTX, 3.5–8 g/m^2	–	94% response rate	

Ara-C, cytarabine; BEAM, carmustine,etoposide, aracytine,melphalan; BOMES, carmustine, vincristine, methotrexate, etoposide, methylprednisolone; CR, complete remission; CYVE, cytarabine, etoposide; DHAP, Dexamethasone, high-dose cytarabine, cisplatin; EFS, event-free survival; FU, follow-up; HCR, hematopoietic stem cell rescue; IC, thiotepa, busulfan, cyclophosphamide; IT, intrathecal; MPV, methotrexate, procarbazine, vincristine; MTV, methotrexate, thiotepa, vincristine; MTX, methotrexate; *n*, number of patients; Os, overall survival; PCV, procarbazine, carmustine, vincristine; PFS, progression-free survival.
*Transplanted patients.

cytarabine (2), 14 responder patients received intensive BEAM and stem cell rescue. CR rate was 60% and 28-month survival rate was 60%.

The protocol used in the present study combined chemotherapy, ASCT, and then radiotherapy. The CR rate was 100%. No major neurotoxicity was observed except in one patient with epilepsy.

The BEAM conditioning regimen was chosen not only because it is the most widely used conditioning regimen in APSCT for systemic NHL, but also because it can be administered relatively safely to patients over the age of 60 yr. Although all of the molecules used in this type of conditioning regimen are able to cross the blood–brain barrier, the final concentration in the brain appears to be insufficient (2). Soussain *et al*. as discussed previously, obtained good results with a conditioning regimen consisting of busulfan, thiotepa, and cyclophosphamide. Thiotepa and busulfan easily cross the blood–brain barrier.

With a CR rate of 100% and relatively low neurotoxicity, the results of this study are fairly encouraging. However, the small number of patients and the relatively short follow-up do not allow statistical interpretation of these results. The low neurotoxicity rate could also be explained by the short follow-up and the relatively young age of patients, as age constitutes the major risk factor for neurotoxicity.

In conclusion, the combination of intensive chemotherapy, ASCT, and radiotherapy does not appear to induce greater toxicity than that observed with the 'conventional' chemotherapy–radiotherapy combination. The choice of conditioning regimen is center dependent, and further studies will probably help to define the optimal regimen. The value of ASCT in the treatment of PCNSL, as first-line treatment, is not currently well defined and should be considered experimental until further, randomized studies with a greater number of patients and longer follow-up are done.

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