ESHAP chemotherapy is efficient in refractory/relapsed primary central nervous system lymphoma: report of four cases

Rodica Ungur1,2  
Adrian Tempescul3  
Christian Berthou3  
Cristina Bagacean1,2  
Doinel Radeanu1  
Adriana Muresan1  
Mihnea Zdrenghea1,2

1Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy Cluj, 2Department of Hematology, Ion Chiricuta Oncology Institute, Cluj-Napoca, Romania; 3Department of Clinical Hematology, Institute of Cancerology and Hematology, Brest Teaching Hospital, Brest, France

Abstract: Primary central nervous system non-Hodgkin’s lymphoma is a rare presentation, almost always of diffuse large B-cell type. Although there is no consensus regarding therapy for this condition, induction regimens are based on high-dose methotrexate and consolidation whole-brain radiotherapy, or, more preferred recently, blood–brain barrier penetrating drugs such as etoposide, cytarabine, and alkylating agents like temozolomide, ifosfamide, and lomustine. We present here four cases of relapsed/refractory primary central nervous system lymphoma treated with ESHAP (etoposide, solumedrol, high-dose cytarabine, and platinum) chemotherapy to complete remission, with the eligible patients proceeding to autologous transplantation. We want to draw attention to this interesting, relatively well tolerated, underused therapeutic option, in a setting where treatment options are scarce and evidence-based recommendations are lacking.

Keywords: cerebral lymphoma, PCNSL, refractory, relapsed, platinum

Introduction

Although non-Hodgkin’s lymphoma is a frequent cancer worldwide, primary central nervous system lymphoma (PCNSL) is a rare malignancy, with an incidence of less than 0.5 per 100,000 persons-years in the Western world.1 In more than 90% of cases, it has the histological features of a diffuse large B-cell lymphoma (DLBCL). Because of its low incidence, high grade evidence from large studies is lacking, and current management is based on reports on rather small cohorts. Evidence is even scarcer in the relapsed/refractory setting. The current standard first-line treatment for PCNSL consists of high-dose methotrexate (MTX) in combination with a variety of drugs and consolidation whole-brain radiotherapy, the latter being progressively replaced by chemotherapy.2 For patients relapsing after first-line treatment, intensive chemotherapy with autologous stem cell support is a feasible and relatively safe salvage therapy. For elderly patients, not able to withstand autografting, the second line of treatment is more controversial.

ESHAP (etoposide, solumedrol, high-dose cytarabine, and platinum) chemotherapy has been found to be an effective salvage regimen for nodal B-cell and Hodgkin’s lymphomas and is accepted as an induction treatment before autografting. The regimen includes drugs known to be able to penetrate the blood–brain barrier3 and used for the treatment of cerebral tumors or metastases.

Here, we describe four cases of patients with PCNSL, either relapsed or refractory to first-line treatment, in which the induction with ESHAP chemotherapy allowed the achievement of a complete remission. Autologous stem cell transplantation under...
optimal conditions for the younger patients was thus possible. For the two elder patients, consolidation therapy using the same regimen was continued. The Institutional Review Board does not require ethical approval for case reports. All patients signed informed consent forms.

During a calendar year (2011), we identified four patients. All were HIV negative and treated for PCNSL with standard high-dose MTX therapy using the local protocol: induction therapy consisting of four cycles of MBVP (MTX, carmustine, etoposide, methyl prednisolone) followed by consolidation with three cycles of ifosfamide plus cytarabine and two cycles of cytarabine and etoposide (no radiotherapy), either refractory or relapsed within 2 years after completion of treatment. Patients’ characteristics are presented in Table 1.

At relapse, the patients were given ESHAP chemotherapy every 21 days. Dose adjustment was made for the elder patients, according to the local protocol requiring a 30% reduction of etoposide, cytarabine, and platinum doses for patients with performance status >1. An evaluation by computed tomography (CT) scan or magnetic resonance imaging (MRI) was performed on day 1 of each cycle of chemotherapy. The patients received primary granulocyte colony stimulating factor prophylaxis for neutropenia from chemotherapy. The patients then proceeded to autologous stem cell transplantation (standard BEAM conditioning).

### Table 1 Outcome after ESHAP therapy with and without autologous stem cell transplantation in four patients with relapsed/refractory PCNSL

| Patient | Age (years) | Initial treatment | Status after initial treatment | Localization at relapse | Time to relapse (months) | ESHAP cycles to CR | Outcome after salvage therapy |
|---------|-------------|-------------------|-------------------------------|-------------------------|-------------------------|------------------|-----------------------------|
| 1       | 57          | 4MBVP + 3AraC + Ifo 2AraC + VP16 | Progressive disease | Left parietal | 1 | 2 | In CR, 30 months after ASCT |
| 2       | 62          | 4MBVP + 3AraC + Ifo 2AraC + VP16 | Complete remission | Left parietal | 24 | 1 | Relapsed after 8 months, deceased at 12 months |
| 3       | 78          | 4MBVP + 3AraC + Ifo 2AraC + VP16 | Progressive disease | Suprapeduncular | 1 | 1 | Deceased after 8 months (not lymphoma related) |
| 4       | 70          | 4MBVP + 3AraC + Ifo 2AraC + VP16 | Complete remission | Suprapeduncular | 14 | 2 | Relapsed after 10 months, deceased at 12 months |

Abbreviations: ESHAP, etoposide, solumedrol, high-dose cytarabine, and platinum; PCNSL, primary central nervous system lymphoma; CR, complete remission; ASCT, autologous stem cell transplantation; MBVP, methotrexate, carmustine, etoposide, methyl prednisolone; Ifo, ifosfamide.

It is now well established that the first-line treatment for PCNSL is based on an association of high doses of MTX with other drugs, with or without whole-brain radiotherapy. For refractory or relapsed cases, several regimens have been proposed. Treatment with temozolomide, topotecan, carboplatin, and cytarabine achieve response rates of 26%–37%. Autologous stem cell transplantation is an important therapeutic option in these patients, allowing for an increase in overall survival.

Cisplatin-based ESHAP chemotherapy has for a long time demonstrated efficacy in refractory/relapsed patients with DLBCL. Soussain et al proved in a cohort of 65 patients with relapsed/refractory DLBCL (including 27 patients with bone marrow and CNS involvement, but not PCNSL) that ESHAP chemotherapy is effective, allowing for peripheral...
stem cell harvest and autologous stem cell transplantation.\textsuperscript{10} It has also been proven that ESHAP chemotherapy could be administered in elderly patients without significant toxicity.\textsuperscript{11} Platinum-based chemotherapy is also effective in infant brain tumors.\textsuperscript{12}

Use of ESHAP in PCNSL has been rarely reported, most notably in a French retrospective study of 22 immunocompetent patients with relapsed/refractory disease, of which five received rituximab (R)-ESHAP, two obtaining a complete and one a partial remission. The rest received dexamethasone, high dose aracytine, and cisplatin +/-R, to an overall complete remission rate of 27%.\textsuperscript{13} In our patients, the use of ESHAP chemotherapy resulted in rapid regression of symptoms and disappearance of lesions observed in CT or MRI scans. The treatment was well tolerated; the two younger patients were stem cell mobilized, and then autologous stem cell transplantation was performed in optimal conditions. The two elderly patients continued with two additional cycles of the same regimen as consolidation therapy.

We saw a remarkable effectiveness of ESHAP chemotherapy in our patients, previously treated with high doses of MTX, cytarabine, etoposide, and corticosteroids. Although this is a report of a small series of patients, we propose ESHAP chemotherapy as an efficient and well-tolerated salvage regimen, ideally followed by autologous stem cell transplantation, in relapsed/refractory primary CNS lymphoma. Obviously, as with all PCNSL treatments, there is a need for larger, prospective trials to yield higher grade evidence allowing for stronger recommendations.

Acknowledgments
Dr R Ungur acknowledges support under the frame of European Social Fund, Human Resources Development Operational Program 2007–2013, Project No.POSDRU/159/1.5/S/138776, Drs Zdrenghea and Bagacean from Grant CNCS-UEFISCDI, Project Number PN-II-RU-PD-2011-3-0277, and Dr Zdrenghea from Grant 1494/2014 from the University of Medicine and Pharmacy Cluj. The sponsors had no involvement in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

Disclosure
The authors report no conflicts of interest in this work.

References
1. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 2011;105(9):1414–1418.
2. Rubenstein JL, Gupta NK, Mannis GN, Lamarre AK, Treseler P. How I treat CNS lymphomas. Blood. 2013;122(14):2318–2330.
3. Muldoon LS, Soussain C, Jahnke K, et al. Chemotherapy delivery issues in central nervous system malignancy: a reality check. J Clin Oncol. 2007;25(16):2295–2305.
4. Olson JE, Janney CA, Rao RD, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. Cancer. 2002;95(7):1504–1510.
5. O’Neill BP, Decker PA, Tieu C, Cerhan JR. The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin’s lymphoma. Am J Hematol. 2013;88(12):997–1000.
6. Montesinos-Rongen M, Siebert R, Deckert M. Primary lymphoma of the central nervous system: just DLBCL or not? Blood. 2009;113(1):7–10.
7. Sierra del Rio M, Rousseau A, Soussain C, Ricard D, Hoang-Xuan K. Primary CNS lymphoma in immunocompetent patients. Oncologist. 2009;14(5):526–539.
8. Soussain C, Hoang-Xuan K, Taillandier L, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societe Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. J Clin Oncol. 2008;26(15):2512–2518.
9. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP – an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol. 1994;12(6):1169–1176.
10. Soussain C, Souleau B, Gabarre J, et al. Intensive chemotherapy with hematopoietic cell transplantation after ESHAP therapy for relapsed or refractory non-Hodgkin’s lymphoma. Results of a single-centre study of 65 patients. Leuk Lymphoma. 1999;33(5–6):543–550.
11. Aviles A, Neri N, Huerta-Guzman J, de Jesus Nambo M. ESHAP versus rituximab-ESHAP in frail patients with refractory diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk. 2010;10(2):125–128.
12. Fouladi M, Gururangan S, Moghrabi A, et al. Carboplatin-based primary chemotherapy for infants and young children with CNS tumors. Cancer. 2009;115(14):3243–3253.
13. del Rio MS, Chouquet S, Hoang-Xuan K, et al. Platine and cytarabine-based salvage treatment for primary central nervous system lymphoma. J Neurooncol. 2011;105(2):409–414.