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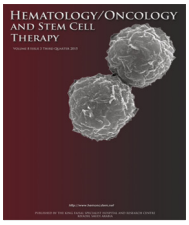

Treatment with methotrexate, rituximab, and cytosine arabinoside followed by autologous stem cell transplantation in primary central nervous system lymphoma: A single-center experience

Pinar Ataca Atilla *, Erden Atilla, Sinem Civriz Bozdag, Meltem Kurt Yuksel, Selami Kocak Toprak, Pervin Topcuoglu, Taner Demirer, Osman Ilhan, Onder Arslan, Gunhan Gurman, Muhit Ozcan

Department of Hematology, School of Medicine, Ankara University, Ankara, Turkey

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Abstract
Objective/Background: Primary central nervous system lymphoma (PCNSL) is associated with worst prognosis compared with other aggressive non-Hodgkin's lymphomas. However, recent trials have demonstrated that long-term progression-free survival can be achieved by immunochemotherapy. Our goal is to present our experience in aggressive PCNSL in this study.
Methods: We retrospectively evaluated the clinical features and management of 13 PCNSL patients who were diagnosed and treated between 2006 and 2015.
Results: Nine patients received rituximab (R) 375 mg/m^2/day on Day 1, methotrexate (MTX) 3.5 g/m^2/day and cytosine arabinoside (ARA-C) 4.4 g/m^2/day on Day 2, as well as ARA-C 4.4 g/m^2/day on Day 3 every 28 days, and underwent autologous stem cell transplantation. Two patients received procarbazine instead of ARA-C. One patient relapsed, and allogeneic hematopoietic stem cell transplantation was performed. All nine patients are followed in complete remission. Two of 13 patients received one course of MTX and 36—45 Gy radiotherapy and

* Corresponding author at: Department of Hematology & BMT Unit, School of Medicine, Ankara University, Cebeci Hospital, Dikimevi, Ankara 06590, Turkey.
E-mail address: pinar@ataca.tk (P.A. Atilla).

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died. One patient with renal transplantation had progressive disease and died. Grade 3–4 hematological toxicity was detected in 11 (85%), Grade 3–4 mucositis in 11 (85%), and febrile neutropenia in 12 (92%) patients. The median overall survival in the R–MTX–ARA-C/procarbazine group was 28 ± 16 months.

Conclusion: R–MTX–ARA-C followed by autologous stem cell transplantation seems a promising strategy with high response rates in PCNSL.

Introduction

Primary central nervous system lymphomas (PCNSLs) account for approximately 4% of primary central nervous system tumors, and are relatively rare extranodular non-Hodgkin's lymphomas. PCNSL has an aggressive course; median survival of untreated patients is 3 months [1]. There is an increasing incidence of about 1/100,000 per year, and 60% of the patients are older than 60 years at diagnosis [2,3]. Two international prognostic scores have been evolved to predict the outcome in PCNSL. The International Extranodal Lymphoma Study Group (IELSG) score is based on lactate dehydrogenase, age, and ECOG and involvement of deep brain structures and cerebrospinal fluid protein concentration [4]. The Memorial Sloan Kettering Cancer Center score also divides patients into three groups according to age and Karnofsky performance status [5].

In the absence of prospective data, whole-brain irradiation (WBRT) had been the first treatment choice with immediate responses; however, patients rapidly deteriorate and suffer with delayed neurotoxicity [6]. There are conflicting data in the literature for surgical cytoreduction. Surgical cytoreduction was found to have no effect on overall survival (OS) since surgery was not recommended as the first-line therapy in several studies [7,8]. The combination immunochemotherapy regimens used recently for the induction consist of high-dose methotrexate (MTX), cytosine arabinoside (ARA-C), thiotepa, ifosfamide, mitoxantrone, and vincristine with or without rituximab (R). For consolidation or relapsed setting, studies evaluated the role of autologous stem cell transplantation (auto-SCT), which appears promising [6]. In this study, our aim is to demonstrate our PCNSL treatment strategy.

Patients and methods

We retrospectively evaluated the clinical features and management of 13 PCNSL patients who were diagnosed and treated at Ankara University's Department of Hematology and Ankara Medicana Hospital between 2006 and 2015. Patient and transplantation data were collected using electronic clinical records. The patients were scored by the IELSG system at diagnosis, followed by serial magnetic resonance imagining studies for response [4]. The results were evaluated by SPSS 20.0 (released 2011; IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, NY, USA).

Results

Seven of the 13 patients were male. The mean age of the group was 51.6 ± 16.8 years (range 28–75 years). Their performance status at diagnosis due to the ECOG was indicated with a score of 0, 1, 2, and 3 for three (23%), six (46%), one (8%), and three (23%) patients, respectively. The most common symptoms at diagnosis were headache in six (46%), dizziness in two (15%), and memory loss in four (31%) patients, and lumber pain in one patient (8%). Diagnosis was established by craniotomy in eight patients (61%), stereotactic biopsy in four patients (31%), and cerebrospinal fluid analysis in one patient (8%). Cerebral/spinal parenchyma was involved in seven (54%) patients, while six (46%) patients had deep brain involvement. Eleven (85%) patients had brain edema, while 10 (77%) had mass effect. Multiple lesions were detected in eight (62%) patients. The mean serum lactate dehydrogenase level was 309 U/L (range 102–555 U/L). Six patients (46%) had a high cerebrospinal fluid protein level. All our patients were HIV negative.

Nine patients received R 375 mg/m^2/day on Day 1, MTX 3.5 g/m^2/day and ARA-C 4.4 g/m^2/day on Day 2, and ARA-C 4.4 g/m^2/day on Day 3 every 28 days. One geriatric patient and one patient with renal transplantation received procarbazine 100 mg/day instead of ARA-C. Of nine patients, five received four cycles and four received three cycles, and achieved complete remission. Auto-SCT was performed with cyclophosphamide 4 × 1.5 g/m^2, etoposide 4 × 250–400 mg/m^2, and carmustine 4 × 150–200 mg/m^2 conditioning regimen as consolidation treatment. One patient relapsed after complete remission at the 4th month of auto-SCT. The patient was in stable disease after two cycles of temozolomide and underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) from full matched sibling with 6 × 10^6/kg CD34-positive peripheral blood cells. As a conditioning regimen, this patient received fludarabine, busulfan, and thiotepa following cyclosporine and MTX as a graft versus host disease prophylaxis. The patient was clinically stable and achieved complete remission at the 6-month follow-up with neutrophil engraftment on Day 18 and platelet engraftment on Day 20. All nine patients are followed in complete remission. Two of 13 patients had a high ECOG performance score and received one course of MTX and 36–45 Gy radiotherapy (RT) and died. Two patients received procarbazine instead of ARA-C: one patient with renal transplantation had progressive disease under the fourth course of chemotherapy

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