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PROLONGED SURVIVAL OF PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA AFTER FIRST-LINE INTENSIVE SEQUENTIAL CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background: Nodal peripheral T-cell lymphomas (PTCLs) are infrequent subtypes of non-Hodgkin's lymphomas. The WHO classification recognizes three subgroups of nodal PTCL: peripheral T-cell lymphoma not otherwise specified (PTCL, NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic lymphoma (AIL). The clinical course is aggressive and despite multiagent chemotherapy, the median survival is about 2 years. Optimal first-line chemotherapy is not established and the role of high-dose therapy with autologous stem cell support is still controversial.

Aim: To analyze the long-term outcome of PTCL patients treated with intensive first-line chemotherapy with high-dose therapy and autologous transplant consolidation.

Method: Sequential chemotherapy protocol consisting of 3 cycles of CHOEP-21-like regimen (PACEBO), 1 cycle of an ifosfamide and methotrexate-based regimen (IVAM) and a priming regimen with high-dose cytosine arabinoside (HAM). Consolidation was provided with myeloablative conditioning (BEAM 200) and autologous stem cell support. Eighty-four patients with aggressive high-risk lymphoma were treated with the sequential protocol from 2000 to 2007 in our institution. Here we report our experience with 18 patients with nodal PTCL (10 PTCL, NOS; 3 ALCL, ALK-negative; 2 ALCL, ALK-positive; 2 ALCL, unknown ALK status; 1 AIL).

Results: Eleven (61 %) patients achieved complete remission, 3 (17 %) partial remission and 4 (22 %) patients failed the procedure. The overall response rate was 77.8 %. After a median follow-up of 25.7 months, nine patients relapsed or progressed (6 PTCL, NOS; 2 ALCL ALK-positive; 1 ALCL ALK-negative; median 14.1 months) and four patients died (lymphoma progression). The relapse was treated with allogeneic stem transplantation in one patient. The 2-year progression-free survival (PFS) was 52 % (95 % CI, 0.27 to 0.76); the 2-year overall survival rate reached 71 % (95 % CI, 0.47 to 0.95).

Conclusion: Our results show that intensive first-line chemotherapy with high-dose therapy and autologous transplant consolidation offers a chance for long-term survival in patients with chemosensitive PTCL.

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are infrequent types of non-Hodgkin's lymphomas (NHLs). In Western countries they represent about 7 % of NHLs[1,2]. The incidence of nodal T-cell lymphomas based on the data from the Czech Lymphoma Study Group (CLSG) registry is 6 % (211 out of 3518 patients)[3]. The World Health Organization (WHO) classification recognizes three subgroups of nodal PTCLs: peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic lymphoma (AIL)[4]. Current conventional treatment modalities do not dramatically improve the outcome of patients and 5-year overall survival still remains between 30 % and 35 % using standard chemotherapy with second- and third-generation regimens[5,6,7]. The role and timing of high-dose therapy with autologous stem cell support (ASCT) remains unclear – some studies have confirmed the survival advantage of ASCT[8,9] while others produced inconsistent results[10,11]. Data from the Czech national registry of (autologous) hematopoietic stem cell transplantations and the CLSG database show an overall survival (OS) of 3 years in 74 % of PTCL patients while conventionally treated patients have a median overall survival of as few as 33 months[12].

The objective of our retrospective single-center study was to analyze the treatment efficacy of a novel intensive first-line chemotherapy protocol with consolidation with high-dose therapy and autologous stem cell transplantation in unselected patients with nodal PTCL.

PATIENTS AND METHODS

Here we report our experience with 18 patients with nodal PTCL (10 PTCL, NOS; 3 ALCL, ALK-negative; 2 ALCL, ALK-positive; 2 ALCL, unknown ALK status; 1 AIL) who were diagnosed in our center between the

Table 1. Patient baseline clinical characteristics. (n = 18)

Sex (male-to-female ratio)	2 : 1
Median age (range)	59 years (29–64)
Advanced disease stage (III + IV)	13 patients (72 %)
Extranodal involvement	13 patients (72 %)
Bone marrow involvement	5 patients (27.8 %)
Elevated lactate dehydrogenase level	4 patients (22 %)
IPI score (0–1 vs. ≥ 2)	5 vs. 13 patients
Median follow-up	25.7 months

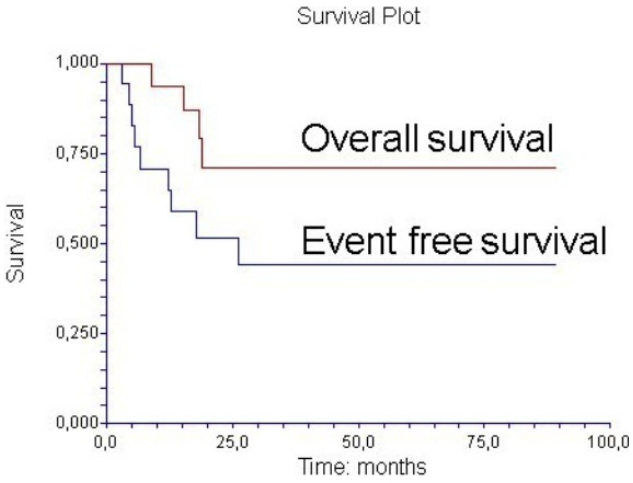

Fig. 1. Survival curves of 18 PTCL patients.

years 2000 and 2007. All biopsies were reviewed by a reference pathologist and final diagnoses were made in compliance with the published WHO classification of lymphoid tumours[4]. The median age at diagnosis was 43 years, 17 patients underwent the protocol as first-line therapy and one as salvage therapy. Twelve patients received first-line high-dose therapy and autologous transplant consolidation; two patients were consolidated with allogeneic stem cell transplantation with reduced-intensity conditioning.

Treatment strategy

The sequential chemotherapy protocol consists of 3 cycles of CHOEP-21-like regimen (PACEBO), 1 cycle of an ifosfamide and methotrexate-based regimen (IVAM) and a priming regimen with high-dose cytosine arabinoside (HAM). Consolidation is provided with myeloablative conditioning (BEAM 200) and autologous stem cell support. A total of 84 patients with aggressive high-risk lymphoma were treated with this sequential protocol from 2000 to 2007 in our institution.

The PACEBO regimen was administered as follows: doxorubicin 40 mg/m^2 intravenously day 1, cyclophosphamide 850 mg/m^2 intravenously day 1, etoposide 200 mg/m^2 intravenously day 1, bleomycin 10 mg/m^2 intravenously day 8, vincristine 1.4 mg/m^2 (maximum 2.0 mg) intravenously day 8 and prednisone 40 mg/m^2 orally days 1 to 14. The IVAM regimen consisted of ifosfamide 1500 mg/m^2 intravenously days 1 to 5, etoposide 150 mg/m^2 intravenously day 1 to 3, cytosine arabinoside 100 mg/m^2 intravenously day 1 to 3, methotrexate 3 g/m^2 intravenously day 5, mesna prophylaxis 1200 mg intravenously days 1 to 5, leucovorin rescue 25 mg/m^2 intravenously from day 6/7 until the plasma methotrexate level was below 0.05 µmol/l. The HAM regimen was administered as follows: cytosine arabinoside 2 g/m^2 twice daily intravenously days 1 and 2, mitoxantrone 10 mg/m^2 days 2 and 3. Stem cell mobilization was performed with 12 µg/kg of filgrastim given subcutaneously twice daily. The BEAM 200 conditioning regimen dosage was standard as previously published.

The treatment responses – complete response (CR), unconfirmed complete response (uCR), partial response (PR), stable disease and progressive disease – were defined according to the International Workshop NHL Response Criteria published by Cheson et al[19].

Statistical methods. Our data were analyzed using the Statistical Package for the Social Sciences (SPSS)[20]. Overall survival (OS) was defined as the time from first treatment to the date of last follow-up examination (censored) or the date of death (event) from any cause. Progression free survival (PFS) was defined as the date of first treatment to the date of documented disease progression or death (event) or the date of last follow-up examination (censored). The Kaplan-Meier method[21] was used to calculate survival probabilities. The log-rank test was used to compare differences in survival times between patient subgroups. The significance level was set at a p= 0.05; 2-tailed tests were used in all calculations.

The EMBASE and PubMed databases were searched for literature reviews.

RESULTS

We analyzed the data of the 18 patients. The baseline clinical parameters are summarized in Table 1. The median age was 59 years (range, 29–64 years), there was a male preponderance (male-to-female ratio 2 : 1). Most of the patients (n = 13, 72 %) had advanced disease of clinical stages III and IV with extranodal lymphoma involvement. Most frequently, bone marrow was involved (27.8 %). B symptoms were present in half of the patients. More than three quarters of the patients had an ambulatory performance status (PS 0–1, n = 15, 83.4 %). Lactate dehydrogenase (LDH) levels were elevated in 4 cases (>1 X normal value). The International Prognostic Index (IPI)[13, 14] score was available in all patients; 5 patients were classified as low risk (0–1), 5 as low-intermediate risk

(IPI 2) and 8 as high-intermediate or high risk (IPI ≥ 3). The toxicity of the treatment protocol was tolerable. Most commonly, hematologic toxicity and infections of grades III–IV according to the NCI CTC were observed. No treatment toxicity- or transplant-related death occurred. No persistent treatment-related disability or severe organ dysfunction were observed. So far, no secondary malignancies have occurred.

Analysis of response and survival

The overall CR rate was 61 % (n = 11), PR rate 17 % (n = 3) and 4 patients (22 %) had stable or progressive disease after first-line treatment. After a median follow-up of 25.7 months, nine patients relapsed or progressed (6 PTCL, NOS; 2 ALCL ALK-positive; 1 ALCL ALK-negative; median 14.1 months) and four patients died (lymphoma progression). Nine patients are still in CR. In one patient, the relapse was treated with allogeneic stem cell transplantation. The 2-year progression-free survival (PFS) was 52 % (95 % CI, 0.27 to 0.76); the overall survival rate reached 71 % (95 % CI, 0.47 to 0.95).

DISCUSSION AND CONCLUSION

PTCLs still represent a heterogeneous group of aggressive lymphomas with disappointing treatment results. In most cases, conventional chemotherapy either is ineffective or leads only to response with limited duration. Gisselbrecht et al. reported a 5-year OS of 35 % in PTCL patients[7], Escalón et al. published even worse results both in patients treated intensively or with the CHOP regimen (3-year OS of 49 % and 43 %, respectively)[24]. The appropriate dose intensity of chemotherapy and the role of high-dose therapy with ASCT were unclear due to the heterogeneity of the studied sample and frequent inclusion of anaplastic PTCL or B-cell lymphoma subtypes[14,24].

Recently, numerous clinical studies have been published that show variable effects of intensive induction therapy followed by consolidation with high-dose chemotherapy and autologous stem cell transplantation. A large retrospective study carried out by the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation have confirmed the benefit of this treatment modality in patients with AIL, especially if CR was achieved after induction treatment (OS 67 % at 24 months and 58 % at 48 months) (ref.[27]). In contrast, a prospective study by Mercadal et al. showed no clear benefit of aggressive treatment approach in first-line therapy – the use of the high-dose CHOP regimen alternating with the platinum-based ESHAP regimen is associated with significant toxicity and no real increase in the rate of complete remission[28]. Rodríguez reported the effect of early ICE salvage therapy and autologous stem cell transplantation in high-risk PTCL patients, with gallium-positive scan after 3 cycles of treatment with the megaCHOP protocol and an optimistic OS at 3 years of 73 % (ref.[29]). Similarly favorable results are those in Rodríguez's retrospective analysis of AIL patients with a 3-year OS of 60 % (ref.[30]).

According to our experience, a significant number of patients with nodal PTCL may benefit from the sequential treatment protocol and early consolidation with autologous stem cell transplantation. In our group, the overall response rate reached 78 % (CR rate 61 %, PR rate 17 %). The procedure failed in a quarter of the patients. After initial treatment, relapse or lymphoma progression occurred in half of the patients, with a median of 14.1 months. Paradoxically, treatment failed in both patients with ALK-positive ALCL. The 2-year progression-free survival (PFS) was 52 %; the 2-year overall survival rate reached 71 %. The toxicity of the sequential protocol was tolerable. Despite the administration of lower doses of cyclophosphamides and anthracyclines, and the absent platinum-based regimen, the protocol results in treatment outcomes comparable to those achieved by the MegaCHOP/ESHAP regimens.

To conclude, the treatment approach to younger patients with nodal PTCL is not unified. The current first-line treatment procedures range from the classical CHOP schemes, through the MegaCHOP/ESHAP/ICE intensive toxic regimens, to high-dose chemotherapy with autologous stem cell transplantation. The administration of our novel intensive first-line sequential chemotherapy protocol with consolidation with high-dose therapy and autologous stem cell transplantation is a safe and effective treatment modality in patients with nodal PTCL. In about half of the patient population, intensive chemotherapy with autologous stem cell transplantation offers a chance for long-term survival and may lead to improved quality of treatment response or provide time for finding a donor for allogeneic transplantation[11]. Future advances in treating these patients will not be possible without designing prospective studies, introducing immunochemotherapy[26] and implementing new prognostic schemes[16,17] and PET restaging.

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