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. 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). 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). 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. 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 while others produced inconsistent results.

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.

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
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. 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/m² intravenously day 1, cyclophosphamide 850 mg/m² intravenously day 1, etoposide 200 mg/m² intravenously day 1, bleomycin 10 mg/m² intravenously day 8, vincristine 1.4 mg/m² (maximum 2.0 mg) intravenously day 8 and prednisone 40 mg/m² orally days 1 to 14. The IVAM regimen consisted of ifosfamide 1500 mg/m² intravenously days 1 to 5, etoposide 150 mg/m² intravenously day 1 to 3, cytosine arabinoside 100 mg/m² intravenously day 1 to 3, methotrexate 3 g/m² intravenously day 5, mesna prophylaxis 1200 mg intravenously days 1 to 5, leucovorin rescue 25 mg/m² 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/m² twice daily intravenously days 1 and 2, mitoxantrone 10 mg/m² 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.

Statistical methods. Our data were analyzed using the Statistical Package for the Social Sciences (SPSS). 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 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) score was available in all patients; 5 patients were classified as low risk (0–1), 5 as low-intermediate risk

<table>
<thead>
<tr>
<th>Table 1. Patient baseline clinical characteristics. (n = 18)</th>
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<tr>
<td><strong>Sex (male-to-female ratio)</strong></td>
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<tr>
<td><strong>Median age (range)</strong></td>
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<tr>
<td><strong>Advanced disease stage (III + IV)</strong></td>
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<td><strong>Extranodal involvement</strong></td>
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<td><strong>Bone marrow involvement</strong></td>
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<td><strong>Elevated lactate dehydrogenase level</strong></td>
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<td><strong>IPI score (0–1 vs. ≥ 2)</strong></td>
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<td><strong>Median follow-up</strong></td>
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(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 sur-
vival (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 ag-
gressive lymphomas with disappointing treatment results.
In most cases, conventional chemotherapy either is inef-
fic or leads only to response with limited duration.
Gisselbrecht et al. reported a 5-year OS of 35 % in PTCL
patients7. Escalon 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 inclu-
sion of anaplastic PTCL or B-cell lymphoma subtypes14,24.

Recently, numerous clinical studies have been pub-
lished that show variable effects of intensive induction
therapy followed by consolidation with high-dose chemo-
therapy 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 treat-
ment 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 prospec-
tive 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 signif-
cant toxicity and no real increase in the rate of complete
remission24. Rodriguez reported the effect of early ICE
salvage therapy and autologous stem cell transplantation in
high-risk PTCL patients, with gallium-positive scan af-
ter 3 cycles of treatment with the megaCHOP protocol
and an optimistic OS at 3 years of 73 % (ref.28). Similarly
favorable results are those in Rodriguez’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 se-
quential 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 treat-
ment outcomes comparable to those achieved by the
MegaCHOP/ESHAP/ICE 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 transplantation11. Future advances in treat-
ing these patients will not be possible without designing
prospective studies, introducing immunochemistry and
implementing new prognostic schemes26-27 and PET
restaging.

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