*Grzegorz Helbig[1], Tomasz Kandzia[2], Marcin Kubeczko[2], Maria Liszka[2], Klaudyna Machura[2], Małgorzata Makowska[2], Tomasz Oleksy[2], Sławomira Kyrcz-Krzemień[1]

Autologous stem cell transplantation (ASCT) as a remission consolidation offers a durable survival benefit in patients with peripheral T-cell lymphomas (PTCL)

Autologiczne przeszczepienie komórek macierzystych (ASCT) jako konsolidacja remisji wydłuża przeżycie chorym z chłoniakiem z obwodowych limfocytów T (PTCL)

[1]Department of Hematology and Bone Marrow Transplantation, Silesian Medical University, Katowice
Head of Department: Prof. Sławomira Kyrcz-Krzemień
[2]Students Research Group, Department of Hematology and Bone Marrow Transplantation, Silesian Medical University, Katowice
Head of Department: Prof. Sławomira Kyrcz-Krzemień

Summary

Introduction. Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous group of malignancies which are characterized by an aggressive disease course and a poor outcome after conventional chemotherapy.

Material and methods. We analyzed the results of ASCT in 29 patients with advanced stage PTCL. Patients were transplanted after achieving first complete or partial remission after conventional chemotherapy.

Results. Twenty nine patients (15 male and 14 female) at a median age at diagnosis of 45 years (range 20-66 years) were analyzed. The study cohort included 13 with PTCL unspecified (PTCL-U) and 16 patients with anaplastic large cell lymphoma (ALCL). Most patients had advanced disease stage at diagnosis (III and IV Ann-Arbor) and B symptoms. International prognostic index (IPI) ≥ 2 was demonstrated in 10 PTCL-U and 6 ALCL patients. Induction chemotherapy consisted of a median of six CHOP cycles (range 1-10). The median number of all cycles before ASCT was 8 (range 3-20) and 7 (range 3-18) for PTCL-U and ALCL, respectively. The disease status at transplant was as follows: complete remission (CR; n = 8) and partial remission (PR; n = 5) for PTCL-U and 8 CR and 8 PR for ALCL. Conditioning regimen before ASCT consisted of CBV and BEAM for 15 and 14 patients, respectively. Among 29 transplanted patients, 7 died due to disease progression. 22 patients remain in CR. The 3-year probability of the overall survival (OS) and progression-free survival (PFS) for whole group were 79 and 70%, respectively.

Conclusions. We have confirmed that ASCT as consolidation therapy for PTCL is a safe and efficient procedure.

Key words: autologous stem cell transplantation, peripheral T-cell lymphoma, anaplastic large cell lymphoma, remission

Streszczenie

Wstęp. Obwodowe chłoniaki z limfocytów T (PTCL) obejmują heterogenną grupę nowotworów złośliwych o agresywnym przebiegu i złym rokowaniu przy zastosowaniu konwencjonalnej chemioterapii.

Materiał i metodyka. Dwudziestu dziewięciu chorych w zaawansowanych stadiach PTCL zostało poddanych zabiegowi autologicznego przeszczepienia komórek macierzystych (ASCT). Pacjenci byli transplantowani po uzyskaniu pierwszej bądź kolejnej całkowitej remisji (CR) lub częściowej odpowiedzi (PR) uzyskanej po konwencjonalnej chemioterapii.

Wyniki. Analiza objęła 29 pacjentów (15 mężczyzn i 14 kobiet) w medianie wieku 45 lat (zakres 20-66) w momencie postawienia rozpoznania. W badanej grupie znalazło się 13 chorych z obwodowym chłoniakiem z limfocytów T nieokreślonym (PTCL-U) i 16 z anaplastycznym chłoniakiem z dużych limfocytów T (ALCL). U większości pacjentów obserwowano znaczny stopień zaawansowania klinicznego (III lub IV) oraz obecność objawów B. Międzynarodowy wskaźnik rokowniczy IPI ≥ 2 odnotowano u 10 pacjentów z PTCL-U i 6 z ALCL. W chemioterapii indukcyjnej zastosowano schemat CHOP (mediana liczby cykli 6, zakres 1-10). Mediana liczby cykli chemioterapii przed ASCT wynosiła 8 (zakres 3-20) dla PTCL-U i 7 (zakres 3-18) dla ALCL. Status choroby w momencie przeszczepienia był następujący: 8 CR i 5 PR w grupie PTCL-U oraz 8 CR i 8 PR u chorych z ALCL. W kondycjonowaniu przed ASCT zastosowano schemat CBV lub BEAM, odpowiednio u 15 i 14 pacjentów. Spośród

29 chorych poddanych transplantacji, 7 zmarło z powodu progresji choroby. W CR pozostaje 22 pacjentów. Prawdopodobieństwo 3-letniego całkowitego przeżycia (OS) oraz przeżycia wolnego od choroby (DFS) wynosi odpowiednio 79 i 70%.

Wnioski. Wyniki naszej analizy potwierdzają, że ASCT jako leczenie konsolidujące remisję u chorych z PTCL jest bezpieczną i skuteczną opcją terapeutyczną.

Słowa kluczowe: autologiczna transplantacja komórek macierzystych, chłoniak z obwodowych limfocytów T, chłoniak anaplastyczny z dużych komórek, remisja

INTRODUCTION

The peripheral T cell lymphomas (PTCL) comprise a heterogeneous group of malignancies accounting for 10% of all lymphomas. The most common types of PTCL are PTCL-unspecified (PTCL-U) and anaplastic large cell lymphoma (ALCL). ALCL is additionally characterized by the presence or absence of the anaplastic lymphoma kinase (ALK) protein. The patients with ALK-positive ALCL have superior outcome when compared with ALK-negative ALCL and PTCL-U. The latter have aggressive clinical course, patients are usually diagnosed in later disease stage and present with B symptoms. The probability of 5-year disease-free survival (DFS) is estimated to be less than 30% with conventional chemotherapy (1, 2). Current standard of care for PTCL remains to be defined. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen has been established as first-line therapeutic option. Its use resulted in high proportion of responses but relapses were frequently observed (3). High dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been offered as consolidation for patients in first remission as well as for relapsed/ /refractory disease. The long-term results are encouraging for patients transplanted in complete remission with the 5-year overall survival (OS) as high as 68%. Therefore it might be appropriate to offer ASCT especially in this setting (4). Herein we report the long-term results of ASCT as a consolidation for PTCL patients transplanted in complete or partial response.

PATIENTS AND METHODS

Patients selection and characteristics

Twenty nine patients (15 male and 14 female) at median age of 45 years (range 20-66) were submitted to ASCT in our center between 2000-2010. The management of patients after diagnosis followed common standards, but due to the fact, that some patients were referred for transplantation from other centers, not all data were available for all patients. A histological diagnosis was established by the local pathologist and the following subtypes were present: PTCL-U (n = 13) and ALCL ALK negative or unknown (n = 16). The disease stage was evaluated according to the Ann Arbor staging system. The diagnostic work-up included physical examination, blood and serum analysis, chest X-ray, computed tomography of the neck, chest, abdomen and pelvis. Bone marrow biopsy was taken at diagnosis and then repeated at the time of transplant. Patients were eligible for ASCT if they fulfilled the following criteria: 1) first or subsequent complete or partial remission after conventional chemotherapy; 2) ECOG status 0 to 2; 3) age < 70 years and 4) adequate hepatic, renal and cardiac function. All patients signed informed consent approved by local ethical committee. The clinical characteristics of patients was presented in table 1.

Table 1. Patients characteristics.

Parameter	PTCL-U (n = 13)	ALCL (n = 16)	P value
Age (range)	46 (24-61)	39 (20-66)	n.s.
Sex (M/F)	6/7	8/8	n.s.
Ann Arbor stage III-IV	11	10	n.s.
B symptoms	11	11	n.s.
IPI ≥ 2	10	6	n.s.
WBC count (x 10^9/L; range)	5.9 (2.5-25.3)	5.9 (2.6-16.2)	n.s.
Hgb concentration (g/dL; range)	11 (7.3-13.9)	12.2 (8.2-14.7)	n.s.
PLT count (x 10^9/L; range)	179 (34-261)	267 (161-683)	n.s.
Enlarged mediastinal lymph nodes	6	7	n.s.
Enlarged abdominal lymph nodes	6	4	n.s
Hepatomegaly	4	4	n.s.
Splenomegaly	7	4	n.s.
Median number of prior chemotherapy cycles (range)	8 (3-20)	7 (3-18)	n.s.
Median lines of chemotherapy (different regimens) 1. 2. 3.	 7 6 0	 11 3 2	n.s.
Prior radiotherapy	0	3	n.s.

Legend: IPI = international prognostic index; WBC = white blood cell; Hgb = hemoglobin; Plt = platelet; PTCL-U = peripheral T-cell lymphoma-unspecified; ALCL = anaplastic large T-cell lymphoma.

TREATMENT

Induction chemotherapy was uniform and consisted of CHOP regimen in all studied patients. Eleven patients were given second-line regimens including different, usually not anthracycline-based chemotherapeutic schema. Mobilized peripheral blood was the source of stem cells for ASCT in all patients. The most frequently used regimens for mobilization was IVE (ifosfamide, etoposide, epirubicin) plus G-CSF 10 ug/kg starting

from day 5 until the last day of apheresis. The number of 2 x 10^6 CD34-positive cells/kg was considered sufficient to ASCT, but in 2 patients the number of transplanted CD34-positive cells was below this threshold. The apheresis product was processed, frozen to -85 C, stored and re-infused after conditioning completed. The preparative regimens included CBV (cyclophosphamide, BCNU, etoposide) in 15 and BEAM (BCNU, cytarabine, etoposide, melphalan) in 14 patients.

RESPONSE CRITERIA

The response to therapy was evaluated at 1, 3 and 6 months after ASCT and 6 months thereafter. CR was defined as a disappearance of all disease-related symptoms and measurable lesions for at least 4 weeks; PR was defined as a > 50% decrease in the sum of the products of the two largest diameters of all measurable lesions for at least 4 weeks. A progressive disease was defined by any increase > 25% in the sum of the diameter of any measurable lesions or the appearance of a new lesion.

STATISTICAL METHODS

The probability of overall survival (OS) and progression-free survival (PFS) were calculated according to Kaplan-Meier method. All calculations were made from the date of transplantation. Comparisons between the variables were carried out by log-rank test. All variables found to have P value < 0.1 in univariate analysis were considered to be candidates for the stepwise Cox regression model. Statistical significance was defined at a P value <0.05. Transplant-related mortality (TRM) was defined as death within 100 days of high-dose therapy not related to the disease, relapse and progression.

RESULTS

Cell dose and engraftment

The median number of transplanted nucleated cells was 3.31 x 10^8/kg (range 1.41-13.4) and the median number of CD34-positive cells was 5.7 x 10^6/kg (range 1.14-17.2). All patients engrafted. The median time to neutrophil recovery was 13 days (range 10-18) and platelet count > 50 x 10^9/L was achieved after median of 16 days (range 9-33). There was no statistically significant difference in terms of the number of transplanted NC, CD34-positive cells and time to neutrophil and platelet recovery between PTCL-U and ALCL patients. One patient died within 100 days after transplant.

Adverse events and supportive care

Seventeen patients experienced infections during the period of post transplant pancytopenia. Grade 3 or 4 mucositis occurred in 8 patients and it was the most frequent complication. One patient developed severe pneumonia, but recovered soon after neutrophil increase. There was no difference in terms of the frequency of infections between PTCL-U and ALCL.

Median hospitalization time was 25 days (range 17-48) from the date of transplantation. No difference was found between PTCL-U and ALCL. Median number of red blood cell (RBC) and platelet (PLT) transfusions were 2 (range 0-7) and 2 (range 0-5), respectively. Median number of days on cytokine (G-CSF) was 0 (range 0-11). Details on transplant-related factors were listed in table 2.

Table 2. Transplant-related factors.

Parameter	PTCL-U (n = 13)	ALCL (n = 16)	P value
NC median cell dose (range)	4.1 (1.4-13.4)	3.2 (1.7-9.4)	n.s.
CD34 (+) median cell dose (range)	5.7 (1.1-14)	5.5 (1.1-17.2)	n.s.
Engraftment Neutrophils > 0.5 x 0^9/L (median days; range) Platelets > 50 x 10^9/L (median days; range)	 12 (11-17) 16 (10-33)	 14 (10-18) 14 (9-30)	 n.s. n.s.
Infections (all grades)	8	9	n.s.
Disease status at ASCT CR1 PR1	 8 5	 8 8	n.s.
Time from diagnosis to ASCT (median months; range)	12 (4-33)	12 (6-33)	n.s.
Hospitalization since the date of ASCT (median days; range)	26 (20-48)	22 (17-34)	n.s.
RBC transfusion (median; range)	2 (0-7)	1.5 (0-5)	n.s.
PLT transfusion (median; range)	3 (0-5)	1.5 (0-4)	n.s.
G-CSF administration (median; range)	0 (0-11)	0 (0-8)	n.s.

Legend: NC = nucleated cells; ASCT = autologous stem cell transplantation; RBC = red blood cell; PLT = platelet; G-CSF = granulocyte colony stimulating factor; CR = complete remission; PR = partial remission.

Outcome and prognostic factors

At a median follow-up of 46 months from diagnosis (within a range of 16-105 months), 22 of the 29 (76%) patients were alive. The median follow-up from ASCT is 34 months (0,7-94). Seven patients (24%) died due to disease progression and the remaining 22 were in CR. The transplant-related mortality was 3%. The 3-year probability of the overall survival for whole group was 79% (79% for PTCL-U and 80% for ALCL). The probability of progression-free survival (PFS) at 3 years was 70% for whole cohort (66% for PTCL-U and 73% for ALCL). See figures 1-2. The following factors were estimated in univariate analysis for their impact on the probability of OS: age, gender, staging and localization at the time of diagnosis, number of cycles and therapeutic lines before ASCT, disease status at transplantation (CR vs PR). Among them, more than one prior lines of chemotherapy were found to be associated with the lower probability of OS with p value < 0.1. This factor influenced the outcome independently in multivariate analysis (p = 0.01).

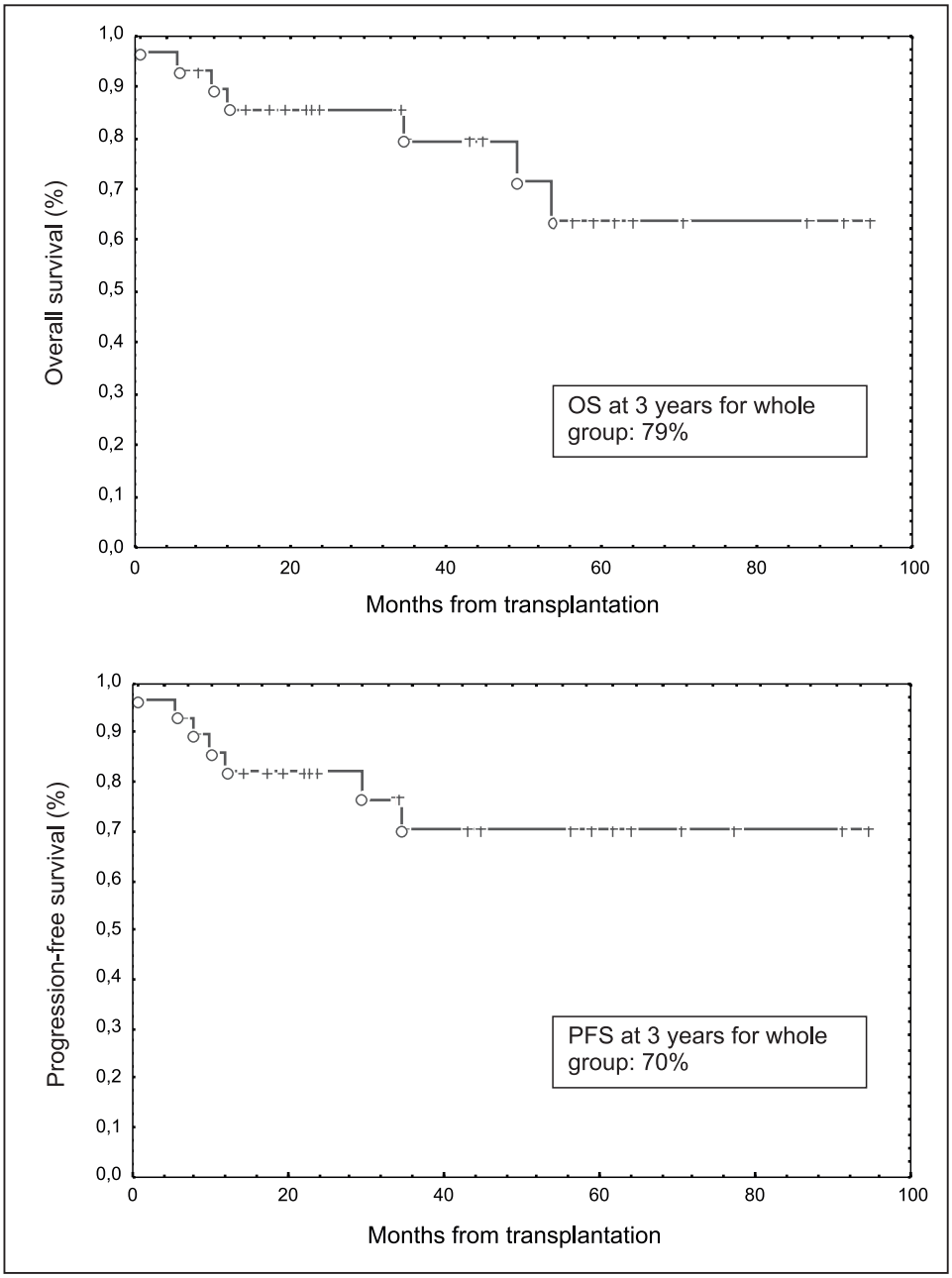

Fig. 1. Overall survival (OS) and progression-free survival (PFS) for whole study group.

DISCUSSION

Our paper reports on the results of ASCT for advanced stage PTCL. Considering the disappointing clinical outcome in PTCL patients treating with conventional chemotherapy, we address the issue if high dose chemotherapy followed by ASCT will improve the long-term results. Our current analysis constitutes a continuation of our previous report which presented the results of ASCT as a consolidation in the first 11 PTCL patients (5). In the majority of up-to-date published data on ASCT for PTCL, the presented results included patients with recurrent or refractory disease and OS and PFS at 5 years varied between 33-37% and 36-24%, respectively. It is noteworthy that TRM was relatively high and exceeded 11%. The reports on the results of ASCT as a salvage regimen for PTCL carried some limitations e.g. there were single-centre experience with small cohort of patients affected by different histological subtypes (6, 7). The major drawback of the published data was the fact that the ALK status remained unknown and it surely influenced the obtained results. There was markedly different outcome between ALK-positive and non-ALK-positive lymphomas. The ALK-positive patients showed a 12-year OS and event-free survival (EFS) rates of 62 and 54% and these results were significantly better than for ALK-negative subset (12-year OS and EFS of 21 and 18%, respectively) (8). Similarly, considering the results reported by us, we must take into account that the expression of ALK was unknown in most of our patients and therefore we did not perform a separate analysis including this subset. Thus, our results were biased by the lack of this information.

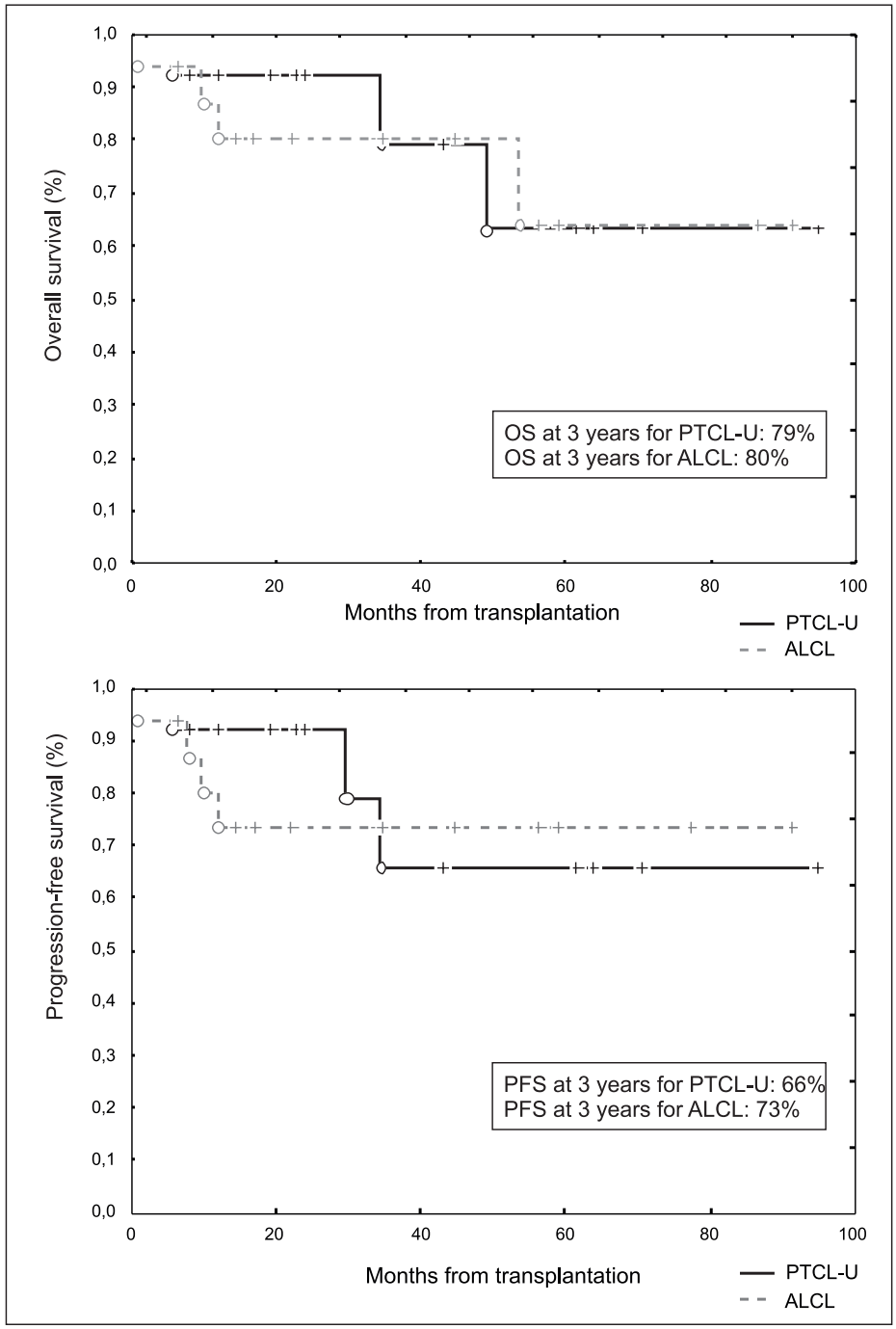

Fig. 2. Overall survival (OS) and progression-free survival (PFS) for patients subgroups.

It may at least partially explain the encouraging ratios of OS and PFS obtained for ALCL group in our analysis. As it was abovementioned (6), a relatively high TRM was a main concern regarding the use of ASCT for PTCL and it resulted from the increased risk of severe infectious complications. However, we should keep in mind that these findings were reported for heavily pretreated patients and ASCT remained a salvage regimen. Considering PTCL patients transplanted in first CR, TRM ranged between 3-5% (4, 8). This rate of TRM was also seen in our study group (3%).

A large retrospective analysis of patients transplanted up-front in CR or PR demonstrated quite encouraging results: for whole study cohort OS and DFS at 5 year were 56 and 60% respectively; these ratios were significantly better for patients transplanted in CR (80 and 79%, respectively for OS and DFS) (9). Similar impressive results were reported by others (10, 11). It was proved that disease status and the number of prior regimens before ASCT impacted the survival (8, 9, 10, 11).

In our study, CR before ASCT was demonstrated in 16 patients (55%) and in fact it was comparable with that reported for patients receiving conventional chemotherapy. On the other hand, long-term follow-up confirmed the superiority of ASCT to CHOP-like regimen: the probability of 5-year OS was 63% and 20-25%, respectively (3, 12). It confirms that consolida-

tion of CR/PR with ASCT offers a survival benefit for PTCL patients. One should remember that the results of retrospective studies have some limitations such as selection bias and treatment heterogeneity.

We should keep in mind that the majority of recently published prospective studies were based on intent-to-treat analysis and the percentage of patients who were able to receive the transplant ranged from 50 to 70% (8, 13). One may conclude that one-third of patients developed early disease progression and therefore they were ineligible for ASCT, but the outcome of patients who finally underwent ASCT was very good (14). These encouraging results were also confirmed by up-to date largest German Study Group. They incorporated ASCT as consolidation after CHOP regimen and they achieved a 3-year OS rate of 71% among patients who were proceeded to transplant (15). In contrast, Italian study demonstrated extremely low 12-year OS and EFS after ASCT for PTCL after excluding ALK-positive patients from analysis (OS and EFS: 21 and 18%, respectively). One should remember that it was intent-to-treat study and drop-out ratio was high (26%) and that these patients were also included in survival analysis (8).

Our data showed a 70% PFS at 3 years with a median follow-up of 34 months from ASCT and the results were comparable with these presented by others (4, 10). Moreover, our patient group seems to be quite large if we consider other studies with PTCL patients transplanted in CR or PR: 29 versus 15 patients reported Chen et al. (10). In our study we analyze some factors which may influence the long-term outcome and more than one prior line of chemotherapy before ASCT was found to be associated with lower probability of OS. Such a factor impacted the survival also in studies published by others (10). Our report, like other series, did not provide the separate results for ALK-positive subset and the encouraging results obtained for ALCL group should be treated with caution. The major conclusion one may draw from prospective studies is early disease progression during induction chemotherapy and therefore the significant proportion of patients are unsuitable for ASCT procedure. The main challenge is therefore the introduction of new more efficient therapeutic regimens.

CONCLUSIONS

In conclusion, ASCT as a consolidation for patients achieving good clinical response (CR or PR) after conventional chemotherapy seems to offer significant outcome benefit with low TRM and manageable side effects.

BIBLIOGRAPHY

1. Vose JM, Armitage JO, Weisenburger D: International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008; 26: 4124-4130.
2. Gisselbrecht C, Gaulard P, Lepage E et al.: Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Grupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998; 92: 76-82.
3. Escalon MP, Liu NS, Yang Y et al.: Prognostic factors and treatment of patients with T cell NHL: the MD. Anderson Cancer Centre Experience. Cancer 2005; 103: 2091-2098.
4. Rodriguez J, Conde E, Gutierrez A et al.: The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. Ann Oncol 2007; 18: 652-657.
5. Stella-Hołowiecka B, Wieczorkiewicz A, Helbig G et al.: Autologiczna transplantacja komórek macierzystych u pacjentów z chłoniakiem z obwodowych limfocytów T – wstępna analiza wyników badań pierwszych 11 pacjentów. Współcz Onkol 2007; 7: 376-380.
6. Rodriguez J, Caballero MD, Gutierrez A et al.: High dose of chemotherapy and autologous stem cell transplantation in patients with peripheral T-cell lymphoma not achieving complete response after induction chemotherapy. The GEL/TAMO experience. Haematologica 2003; 88: 1372-1377.
7. Kewalramani T, Zelenetz AD, Teruya-Feldstein J et al.: Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 2006; 134: 202-207.
8. Corradini P, Tarella C, Zallio F et al.: Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006; 20: 1533-1538.
9. Rodriguez J, Caballero MD, Gutierrez A et al.: High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma : the GEL-TAMO experience. Ann Oncol 2003; 14: 1768-1775.
10. Chen AI, McMillan A, Negrin RS et al.: Long-term results of autologous hematopietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant 2008; 14: 741-747.
11. Nademanee AP, Zain JM, Palmer J et al.: The impact of disease status on the outcome of high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) for peripheral T-cell lymphoma (PTCL). Blood 2006; 108: a 3060.
12. Savage KJ, Chhanabhai M, Gascoyne RD et al.: Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004; 15: 1467-1475.
13. D'Amore F: High-dose therapy and autologous stem cell transplantation in peripheral T-cell lymphomas. Ann Oncol 2005; 16: v15-v26.
14. Lopez-Guillermo A, Mercadal S, Briones J et al.: Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation (ASCT) in previously untreated patients with peripheral T-cell lymphoma (PTCL). Results of a prospective phase II study from the GELCAB. Blood 2005; 106: a2077.
15. Reimer P, Rudiger T, Geissinger E et al.: Autologous stem cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 2009; 27: 106-113.

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Adres/address:
*Grzegorz Helbig
Department of Haematology and Bone Marrow Transplantation,
Silesian Medical University,
Dąbrowski Street 25, 40-032 Katowice
phone: +48 (32) 259-13-10, fax: +48 (32) 255-49-85
e-mail: klinhem@sum.edu.pl