PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED - THE ANALYSIS OF THE DATA FROM THE CZECH LYMPHOMA STUDY GROUP (CLSG) REGISTRY

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Received: October 6, 2006; Accepted: March 23, 2007

Key words: Peripheral T-cell lymphoma/PTCL/Chemotherapy/Survival/Prognosis

Background: Peripheral T-cell lymphoma, unspecified (PTCL-US) is one of the entities from the infrequent family of nodal mature T-cell lymphomas. The clinical course is aggressive, and despite multiagent chemotherapy, the median survival is about 2 years. Published data are limited to retrospective, mostly single-center studies or reviews and usually include more lymphoma subtypes.

Aim: To evaluate the current treatment modalities, clinical outcome and prognostic factors in unselected, new diagnosed patients with PTCL-US in the population of the central european region (Czech Republic).

Method: Czech Lymphoma Study Group is a national scientific organization which provides an on-line database registry which collects a data about almost all new diagnosed lymphoma patients since year 2000. All diagnostic biopsies were reviewed by a reference pathologist.

Results: We analyzed 63 patients with new diagnosis of PTCL-US. The median age was 59 years (25-81), chemotherapy (CHT) was administered in 56 of the 63 patients: anthracyclin-based CHT in 51 %, intensive CHT in 21 % and non-anthracyclin regimen was applied in 13 % of the patients. The overall response rate was 74.4 %, (CR in 57.4 %). After a median follow-up of 19.6 months, 41 % of the patients were in CR, 3.4 % in PR or stable disease and 55 % of the patients died. The estimated survival probability in 3 years was 36 %. Clinical stage (IV) and CR achievement were found to be independent survival predictors in a multivariate analysis.

Conclusions: Although the current treatment modalities are mostly ineffective in PTCL-US, appropriate intensive treatment may lead to prolonged remission but not survival.

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are infrequent types of non-Hodgkin's lymphomas (NHLs). In Western countries they represent about 7 % of NHLs¹, the frequency varied from 1.5 % to 18.3 % in different regions. Highest incidence of PTCLs have been documented in Hong Kong and Taiwan², this fact may reflect increased exposure to oncogenic factors such as human T-cell leukemia virus-1 (HTLV-1) and Epstein Barr virus (EBV) in Asian nations. Published data from the Surveillance, Epidemiology, and End Results (SEER) registries in the USA, which included 114 548 lymphoid neoplasms diagnosed during 1992–2001 show evident increase of T-cell lymphoma incidence (up to 6.4 % per year)(ref.³).

Recently published World Health Organization (WHO) Classification of Tumours⁴ subdivide T-cell lymphomas into predominantly leukemic, extranodal and nodal types. There are three groups of primary nodal PTCLs: anaplastic large cell lymphoma, angioimmunoblastic lymphoma and a broad category of peripheral T-cell lymphoma-unspecified (PTCL-US). PTCLs usually presents with disseminated, often extranodal disease and outcome of the patients is much worse than in B-cell counterpart lymphomas^{5–7}. Current treatment modalities did not dramatically improve outcome of the patients and 5-year overall survival still remains between 30 %–35 % using standard chemotherapy with second and third generation regimens⁷. The role and timing of high dose therapy with autologous stem cell support (ASCT) remains unclear – some studies proved survival advantage of ASCT^{8,9}, others brought inconsistent results^{10,12}. Non-anaplastic T-cell phenotype was found as negative independent prognostic factor both in patients treated with^{10,13}

or without⁷ high dose therapy with ASCT. Promising long-term results were obtained only in younger patients after allogeneic stem cell transplantation¹¹. To predict survival in PTCL patients is widely used International prognostic index (IPI)¹⁴, whose prognostic power was tested in patients with PTCLs with satisfactory results¹⁵. Novel prognostic scores – „T-cell lymphoma specific“ were published in last years. The most predictive ones are: PIT score which include 4 factors (age > 60 years, PS ≥ 2, elevated LDH level, bone marrow attainment)¹⁶ and Novel clinical-pathologic prognostic score (age > 60 years, elevated LDH level, PS ≥ 2, Ki-67 ≥ 80 %)¹⁷.

Objective of our retrospective multicenter study was to analyze the epidemiology, clinical features, prognostic factors, treatment modalities and outcome in the unselected patients with PTCL-US.

PATIENTS AND METHODS

Czech Lymphoma Study Group (CLSG) is a national scientific organization which provides a background for collaboration of hematologists, oncologists and hematopathologists. The Lymphoma registry is an on-line database founded and operated by CLSG to collect a data of all new diagnosed lymphoma patients since year 2000. We analyzed a data of patients with PTCL-US, who were enrolled into our clinical registry between January 2000 and May 2006. No patient selection was done. A data from 3043 patients with non-Hodgkin's lymphomas was obtained during last 6 years. PTCL-US group was represented by 63 cases (2.07 %). The clinical data included age, sex, lactate dehydrogenase (LDH) level, Ann Arbor stage, IPI, extranodal involvement, systemic symptoms,

performance status (PS; ambulatory Eastern Cooperative Oncology PS 0-1 v nonambulatory PS ≥2), presence of systemic (B) symptoms, date of last follow-up, status (alive or dead), type of treatment and chemotherapy protocol.

All biopsies were reviewed by a reference pathologist and final diagnosis was provided in compliance with published World Health Organization (WHO) Classification of Lymphoid Tumours.

Treatment strategies

Most of the patients were treated with CHOP or CHOP-like anthracyclin-based chemotherapy 51 % (32 of 63), 21 % (13 of 63) patients received intensive protocols (MegaCHOP-ESHAP, PROMACE-CytaBOM, Hyper-C-VAD) - intensive protocol was terminated with ASCT in 6 of them. No allogeneic stem cell transplant was indicated. Non-anthracyclin regimen was applied in 13 % (8 of 63) of the cases. No therapy was given in 3 patients due to very poor performance status. 1 patient undergone only radiotherapy and 1 patient only surgical treatment. We have no data about 6 % (4 of 63) of the patients.

The treatment responses: complete response (CR), unconfirmed CR (uCR), partial response (PR) stable disease and progressive disease were classified according the International Workshop NHL Response Criteria published by Cheson et al¹⁸.

Statistical methods. Our data were analyzed with Statistical Package for the Social Sciences (SPSS)¹⁹. 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 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 examina-

Table 1. Patient baseline clinical characteristics (n = 63).

Sex (Male: Female ratio)	1.4 : 1
Age Median (Range)	59 years (25-81)
Advanced Disease stage (III+IV)	48/63 patients (76.2 %)
Extranodal involvement	44/62 patients (70.9 %)
Bone marrow involvement	19/63 patients (30.2 %)
Elevated lactate dehydrogenase level	34/60 patients (56.7 %)
IPI score (0-1 v 2-3)	30 v 27 patients
Median follow-up	19.6 months

Table 2. Clinical characteristics influencing overall survival in multivariate analysis.

	Significance, p	Relative risk (exp. B)	95 % CI, low	95% CI, high
CR achievement	< 0.001	14.038	4.374	45.053
Clinical stage (IV)	0.043	2.456	1.027	5.876

tion (censored). The Kaplan-Meier method²⁰ was used to derive survival probabilities. The log-rank test was used to compare differences in survival times between patient subgroups. Pearson Chi-Square test and the Fisher's Exact Test was used to test the associations of bone marrow involvement, clinical stage, splenic involvement, extranodal involvement, performance status (≥ 2), elevated lactate dehydrogenase level, IPI score, achievement of complete remission, intensive chemotherapy, relapse and CR achievement or exitus probability. Cox proportional hazards regression analysis (Forward Stepwise method)²¹ was used to model the association of prognostic factors and survival time. The p value significance limit was assessed as .05, 2-sided tests were used in all calculations.

The EMBASE and PubMed databases were searched for literature review.

RESULTS

We analyzed a data of the 63 patients, baseline clinical parameters are summarized in Tab. 1. The median age was 59 years (range, 25-81 years), there was a male preponderance (male-to-female ratio 1.4 : 1). Most of the patients had advanced disease clinical stage III and IV: 48 of 63 (76.2 %) with extranodal lymphoma involvement in 70.9 % of the cases. Most frequently was involved bone marrow (30.2 %), followed by spleen (25.4 %). B-symptoms were present in more than half of the patients (53 %). More than two thirds of the patients had ambulatory performance status (PS 0-1, 43 of 63, 68 %). Lactate dehydrogenase (LDH) levels were elevated in more than half of the cases (>1 X normal value, 34 of 60, 56.7 %). IPI score was available in 61 (97 %) of 63 of the patients; 33 patients (54 %) were classified as low risk (0-1), 18 (29.5 %) as intermediate-low (IPI 2) and 10 (16.4 %) as intermediate-high (IPI 3). No patients with high risk IPI score were enrolled into the study.

Analysis of response

In 4 (6.6 %) of the patients the treatment modality is unknown, 3 (4.9 %) patients did not received any treatment. In 9 (14.8 %) of the patients was not the treatment response analyzed. Finally, the treatment response was recorded in 83.9 % (47 of 56) of the patients. Overall CR rate was 57.4 % (27 of 47), PR rate 17 % (8 of 47) and 25.6 % (12 of 47) of the patients had stable or progressive disease after first line treatment. Follow-up data were available in 94.5 % (58 of 63) of the patients. After a median follow-up of 19.6 months 41 % (24 of 58) of the patients were in CR, 3.4 % (2 of 58) in PR or SD and 55 % (32 of 58) of the patients died.

In univariate analysis the factors associated with lower probability of achieving CR were extranodal involvement ($p = 0.019$), low PS ($p = 0.037$), non-intensive chemotherapy ($p = 0.045$) and IPI score 2-3 ($p = 0.035$).

Analysis of survival

After median follow-up (19.6 months), the estimated survival probability of all patients in 3 years was 36 %

Fig. 1. Overall survival of 63 PTCL-US patients (time in months).

Fig. 2. Progression free survival in 59 PTCL-US patients according IPI (time in months). Upper line IPI 0-1, lower line IPI 2-3.

Fig. 3. Progression free survival 55 PTCL-US patients according the intensity of treatment (time in months). Upper line intensive treatment, lower line non-intensive treatment.

(Fig. 1). Fifty percent of the deaths occurred in the first 24 months. Patients with low IPI have longer survival in contrast to those with intermediate low/intermediate high IPI (3-year OS 43 % v 12 %, $p = 0.0052$, Fig. 2). No difference was found in progression free survival (PFS) between these groups. Patients with intensive treatment had longer PFS (2-year PFS 44 % v 18 %, $p = 0.0388$, Fig. 3), but not longer OS. Five factors were significantly associated with reduced overall survival (OS) in univariate analysis: performance status equal or more than 2 ($p = 0.01$), elevated LDH ($p = 0.039$), IPI 2-3 ($p = 0.022$), treatment response worse than CR ($p = 0.001$), relapse ($p = 0.012$). Bone marrow involvement, splenic involvement, extranodal involvement, intensive chemotherapy, sex and age were nonsignificant factors. Two factors (clinical stage, CR achievement) were found to be independent survival predictors in multivariate analysis (Tab. 2).

DISCUSSION AND CONCLUSION

Last years have brought an explosion of a new information about tumor cell origin²² in PTCLs. Expression profiles both on DNA²³ or protein^{17, 24} level were widely studied. The prognostic impact of Epstein - Barr virus positivity of the tumor cells using In Situ Hybridization (EBER-ISH) was confirmed²⁸. New subclassifications of heterogeneous group of PTCL-US were provided by a novel „T-cell lymphoma specific“ prognostic scores^{16, 17}. Unfortunately, none of these advances on the field of pre-clinical research were not translated into better outcome of PTCL-US patients. PTCL-US still represent a heterogeneous group of aggressive lymphomas with disappointing treatment results. Gisselbrecht et al report a 5-year OS for PTCLs 35 %, Escalón et al. published even worse results both in patients treated intensively or with CHOP regimen (3-years OS 49 % v 43 %)(ref.²⁵). The appropriate dose intensity of the chemotherapy and role of high dose therapy with ASCT are still unclear due to heterogeneity of studied populations and frequent inclusion of anaplastic PTCL or B-cell lymphoma subtypes.

Here we have reported a data of unselected group of patients with PTCL-US from the CLSG registry. The overall low incidence of PTCL-US (2.07 %) and also baseline clinical characteristic of the patients correspond with previously published data⁴⁻⁷.

First line treatment was based mostly on CHOP or CHOP-like regimens, less frequently was applied intensive chemotherapy with or without ASCT or non-anthracycline combinations. Overall CR rate was 57.4 %, PR rate 17 % (8 of 47) and 25.6 % (12 of 47) of the patients had stable or progressive disease after first line treatment. Achievement of CR was more frequently achieved using intensive chemotherapy and was associated with lower probability of death. Patients in CR had significantly longer PFS, but not OS. The estimated survival probability of all patients in 3 years was 36 %. Half of the patients died during the first 24 months. Patients with low IPI have longer survival in contrast to those with intermedi-

ate low/intermediate high IPI (3-year OS 43 % v 12 %, $p = 0.0052$). Overall poor survival may be affected by enrolment of the patients without any treatment or with up-front palliative treatment.

We conclude that patients with PTCL-US have one of the worst prognoses among all non-Hodgkin's lymphoma subtypes patients. The current treatment modalities are mostly ineffective or lead only to response with limited duration. The therapy is still based on protocols primarily designed for B-cell lymphomas. Total dose intensity studies were not performed²⁶. No “big step forward“ as observed in the rituximab era in B-cell lymphomas was acquired. The future progress in management of PTCL-US patients must include wide collaboration of all institutions, application of new tissue microarray immunohistochemistry, novel prognostic scores, design of new treatment strategies including chemo-immunotherapy^{5, 27} and allogeneic stem cell transplantation¹¹.

ACKNOWLEDGEMENT

We would like to thank to all collaborating institutions and investigators of the Czech Lymphoma Study Group (CLSG):

Ingrid Vášová, Interní hemato-onkologická klinika, Fakultní nemocnice Brno; Milada Jankovská, Fakultní nemocnice Královské Vinohrady, Praha; Kateřina Kubáčková, Fakultní nemocnice Motol; David Belada, Fakultní nemocnice Hradec Králové; Jan Pirnos, Nemocnice České Budějovice; Katarína Petráková, Masarykův onkologický ústav Brno; Milan Matuška, Fakultní nemocnice s Poliklinikou Ostrava - Poruba; Jana Příbylová, Nemocnice Chomutov; Jiřina Švecová, Nemocnice Tábor; Inge Bolomská, Masarykova nemocnice v Ústí nad Labem; Barbora Otavová nemocnice Benešov u Prahy; Marek Trněný, Všeobecná fakultní nemocnice, Praha; Libuše Novosadová, David Starostka Nemocnice s Poliklinikou Havířov.

This research was supported by the grant of the Ministry of Health of the Czech Republic (IGA MZ ČR: NR 8231-3).

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