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RETROSPECTIVE ANALYSIS OF 23 CASES WITH PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED: CLINICAL CHARACTERISTICS AND OUTCOME

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ABSTRACT

Background and Objective. Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of post-thymic malignancies relatively uncommon in the Western world and their prognosis and therapeutic approach are still not well defined. The aim of this study was to retrospectively analyze the clinical, hematological and histological features at diagnosis, the relevance of the International Prognostic Index and the outcome of a group of 23 patients affected by *peripheral T-cell lymphoma, unspecified* (PTCL-U), according to the *Revised European-American Classification of Lymphoid Neoplasms* (REAL), observed between September 1985 and April 1995 at our Institution.

Methods. Patients were separated into different prognostic groups according to Ann Arbor stage, cell size and International Prognostic Index. All patients had been treated with multiagent combination chemotherapy, mainly CHOP (9 cases) and F-MACHOP (9 cases), and were evaluable for response. The treatment was intensified with allogeneic bone marrow transplantation (BMT) in 1 patient and with autologous BMT in 4 patients.

Results. Median age was 55 (range 18-77) years and 70% of the patients were males. Four patients were in stage II (17%), 5 in stage III (22%) and 14 in stage IV (61%). Patient risk was classified according to the International Prognostic Index as follows: 8 cases (35%) low risk, 2 cases (9%) low-intermediate, 8 cases (35%) high-intermediate, 5 cases (21%) high. Median follow-up time was 20 months (range 2-132). Median progression-free survival (PFS) and overall survival (OS) for all the patients studied were 10 and 34 months, respectively. Stage IV was associated with a poorer response rate and a shorter PFS (median 6 months) and OS (median 32 months). No statistical correlation was found beetwen cell size and overall response (complete + partial remission), PFS (p=0.38) or OS (p=0.59), although a better trend was observed for the large cell group. A less favorable outcome was observed in patients in the high-intermediate + high risk groups, where median PFS and OS were 7 and 24 months, respectively, than in patients in the low + low-intermediate risk groups. No difference in response or outcome was detected between patients treated with the CHOP and the F-MACHOP regimens, while all 5 patients given high-dose chemotherapy and BMT are alive and in CR.

Interpretation and Conclusions. Our experience shows that PTCL-U are rare lymphomas frequently having an aggressive presentation. The response to conventional polychemotherapeutic regimens like CHOP or F-MACHOP is generally poor, especially in those cases with advanced stage and a high-intermediate or high International Prognostic Index. The observation that all five patients who were treated with bone marrow transplantation are alive and in complete remission suggests using this strategy, particularly in young patients with a poor International Prognostic Index.

Key words: peripheral T-cell lymphoma

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of post-thymic malignancies which account for about 10-15 % of non-Hodgkin's lymphomas (NHL) in the Western world. According to the updated Kiel Classification,[1] PTCL were first distinguished into different subtypes and then stratified into two major prognostic groups (high and low grade) by using cell-size criteria. Although the Kiel Classification represents progress with respect to the classification system of the Working Formulation,[2] which is based on clinicopathological parameters, the histological and prognostic distinction of some PTCL is still controversial. This is due to the objective difficulties pathologists have in distinguishing several similar histotypes and to the apparent lack of prognostic value of grading. For these reasons in the recent *Revised European-American Classification of Lymphoid* neoplasm (REAL)[3] these diseases were simply grouped into a single provisional entity defined as *peripheral T-cell lymphoma, unspecified* (PTCL-U). As mentioned above, these lymphomas are relatively uncommon in the

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Western world and their prognosis and the therapeutic approach to them are still not well defined.

We report herein a retrospective analysis of 23 patients with PTCL-U observed in a single institution over a 10-year period, with the aim of evaluating the clinical, hematological and pathological findings at the time of diagnosis, the prognostic relevance of the International Prognostic Index and the outcome of therapy.

Patients and Methods

Patients

Twenty-three consecutive, unselected patients with a documented histological and immunohistochemical diagnosis of PTCL-U according to the REAL classification, observed at the Division of Hematology of the Udine University Hospital (Italy) between September 1985 and November 1995, were retrospectively evaluated (Table 1). Clinical, laboratory and radiological evaluations pre- and post-treatment included: physical examination, thoraco-abdominal CT scans, bone marrow biopsy, blood cell count and differential, liver and kidney function tests and serum lactate dehydrogenase measurement. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale.[4] Patients were staged according to the Ann Arbor staging system.[5] Only patients in stages II to IV were included in this analysis in order to avoid the bias due to the good prognosis of stage I disease. Prediction of the relative risk of death was made according to the International Prognostic Index, developed by the *International non-Hodgkin's Lymphoma Prognostic Factor Project*[6] and based on age, performance status, tumor stage, serum lactate dehydrogenase level and number of extranodal sites of involvement.

Table 1. Clinical, hematological and histological features at diagnosis in 23 patients with PTCL-U.

Characteristics	*No.of patients*	*%*
Total	23	
Median age, yr (range)	55 (18-77)	
Male	16	70
Female	7	30
Performance Status*		
0-1	13	57
2	10	43
3	0	
4	0	
B symptoms	10	43
Lymphadenopathies		
superficial	13	56
mediastinal	10	43
hilar	1	4
abdominal (mesenteric)	3	13
retroperitoneal	9	39
Extranodal involvement	16/23	69
Bone marrow	7	30
Liver	8	34
Skin	4	17
Lung	3	13
Esophagous	1	4
Parotid gland	1	4
Bulky disease	7	30
Elevated LDH serum level (>460 U/L)	11	47
Ann Arbor Stage		
II	4	17
III	5	22
IV	14	61
Cell size°		
Large	7	30
Mixed	8	35
Medium	8	35
International Prognostic Index#		
Low	8	35
Low-intermediate	2	9
High-intermediate	8	35
High	5	21

**According to the ECOG scale; °according to the REAL classification; #according to the International NHL Prognostic Factor Project.*

Histological evaluation

Diagnosis was performed on pathological specimens obtained from lymph nodes fixed in 10% buffered formalin, processed using routine techniques and embedded in paraffin. All cases were reviewed by two pathologists. Three histological groups (large, medium and mixed) were identified according to disease cell size, as proposed by the REAL classification (Table 1). Patients with other T-cell peripheral lymphomas, such as cutaneous T-cell lymphoma, anaplastic T-large cell lymphoma, angioimmunoblastic, angiocentric, intestinal lymphomas and adult T-cell leukemia/lymphoma, were excluded from this study.

Treatment

Most of the patients received the CHOP (9 cases) or the F-MACHOP (9 cases) regimens. The latter includes cyclophosphamide 800 mg/m^2, vincristine 1 mg/m^2, adriamycin 60 mg/m^2, 5-fluorouracil 15 mg/kg, cytosine arabinoside 1000 mg/m^2, methotrexate 500 mg/m^2, prednisone 60 mg/m^2 from days 1 to 14, in a pre-established sequence.[7] Five patients were treated with other regimens of variable intensity (see Table 2). The therapeutic program was intensified with autologous bone marrow transplantation (BMT) in 4 cases that used BAVC as the conditioning regimen (cytosine arabinoside 150 mg/m^2 twice daily, etoposide 150 mg/m^2 twice daily, cyclophosphamide 45 mg/m^2 once daily from day –5 to day –2, and carmustine 200 mg/m^2 on day –4). Allogeneic BMT was performed in 1 case conditioned with busulphan 16 mg/kg and cyclophosphamide 200 mg/kg.

Response criteria

Remission was defined as complete (CR) if there was no evidence of disease for at least 4 weeks following treatment, partial (PR) if there was 50% or more tumor mass reduction and resistant (NR) in the case of less than 50% reduction in the tumor mass.

Statistical analysis

Multivariate analysis of patient response was not performed since the number of patients for each goup was too small. Progression-free survival (PFS) (calculated from the end of the therapeutic program for patients achieving a CR or a PR) and overall survival (OS) (calculated from diagnosis) were evaluated using the Kaplan-Meier test. Comparisons among the different groups were evaluated with the log-rank test. PFS and OS curves were truncated at 3 years.

Results

Analysis of patient characteristics at diagnosis

Clinical, hematological and histological features of the 23 patients at diagnosis are reported in Table 1. Median age was 55 years (range 18 to 77) and males were prevalent (70%); 4 patients (17%) were in stage II, 5 (22%) in stage III and 14 (61%) in stage IV. Ten patients (43%) had B symptoms and 11 (47%) showed elevated LDH serum levels (> 460

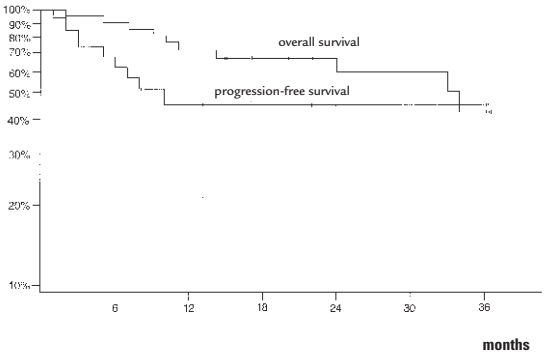

Figure 1. PTCL-U: 3-year PFS and OS of all the patients studied.

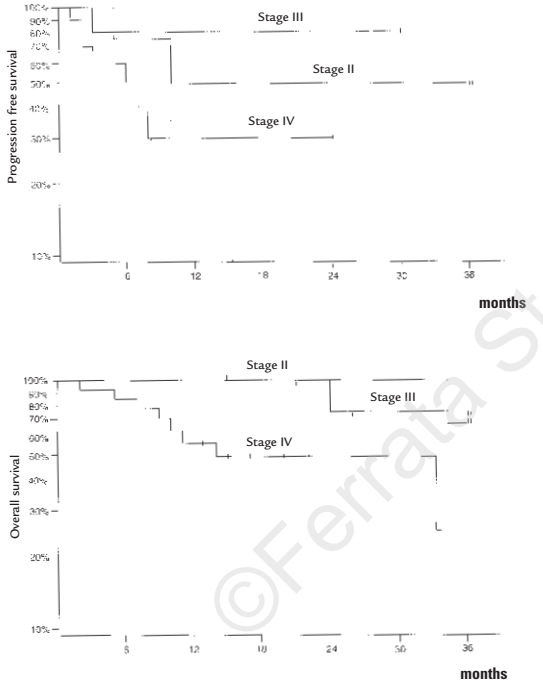

Figure 2. PTCL-U: 3-year PFS and OS according to Ann Arbor stage. The log-rank test of the 3 risk groups was not significant for PFS (p=0.17) or OS (p=0.07).

U/L); 7 patients (30%) presented bulky disease and 16 (69%) displayed extranodal involvement: bone marrow (7 cases), liver (8 cases) and skin (4 cases) were the areas most frequently involved. The International Prognostic Index was evaluable in all cases: 8 patients (35%) had low risk, 2 (9%) low-intermediate, 8 (35%) high-intermediate and 5 (21%) high. Histological evaluation according to the REAL classification showed a pattern of infiltration of large cells in 7 cases (30%), mixed cells in 8 (35%) and medium cells in 8 patients (35%).

Analysis of clinical response

All patients were evaluable for response. Median follow-up time was 20 months (range 2-132). Median PFS and OS for all the patients studied were 10 and 34 months, respectively (Figure 1). Response to therapy and outcome according to Ann Arbor stage, cell size, the International Prognostic Index and the type of treatment are detailed below and are reported in Tables 2 and 3.

Response according to Ann Arbor stage

Overall response (complete + partial remission) was 100% in patients in stages II and III, and 71% in patients in stage IV (Table 3). Three-year PFS and OS curves are shown in Figure 2; median PFS was not reached in patients in stage III, while it was 10 and 6 months in patients in stage II and IV, respectively (p=0.17). Median OS was not reached in patients in stages II and III, and it was 32 months for patients in stage IV (p=0.07).

Response according to cell size

No correlation was found between cell size and overall response, but a higher rate of CR was observed in the large cell group (72%) than in the mixed (50%) and medium (37.5%) cell groups (Table 3). Both PFS and OS were better in the large than in the mixed and medium cell size groups, although the difference was not statistically significant (p=0.38 for PFS and p=0.59 for OS, respectively) (Figure 3).

Response according to treatment

Most of the patients were treated with the CHOP (9 cases) or F-MACHOP (9 cases) regimens. These two groups of patients were comparable for clinical and prognostic characteristics (data not shown). No difference in remission rates resulted from the use of these two regimens: PFS (p=0.66) and OS (p=0.23) (Table 3). Five patients underwent autologous or allogeneic BMT; all of them were in advanced stage (2 cases in stage III and 3 cases in stage IV), and 3/5 were in the low prognostic risk group. At the time of BMT 2 patients were in CR, 1 patient was in stable PR and 2 were in progression. As previously mentioned, 1 patient was transplanted from his HLA-identical sibling donor, while the remaining 4 were reinfused with autologous marrow. All 5 patients are currently in complete remission with disease-free survivals of 8+, 8+, 24+, 27+, 30+ months and an overall survival of 20+, 22+, 36+, 38+, 40+ months, respectively (Table 2).

Response according to the International Prognostic Index

Due to the small number of cases, patients with low + low-intermediate risk were grouped together and compared to those with high-intermediate +

Table 2. PTCL-U: patient characteristics, treatment and outcome.

Pts.	Sex/age	AA stage	II	Cell size	Treatment	Response	PFS (mos.)	OS (mos.)
K.A.	M/18	II A	L	large	LAL 0288	RC	78+	91+
Z.G.	F/58	II A	L	medium	CHOP	RP	10	34
P.D.	F/39	II A	L	medium	CVP	RC	128+	132+
M.M.	F/18	II B	L	large	F-MACHOP	RP	5	15+
M.G.	M/68	III A	HI	mixed	CHOP	RC	22+	26+
T.A.	F/59	III B	HI	mixed	CHOP	RP	13+	21+
G.I.	M/56	III A	HI	large	F-MACHOP ->	RC	4	/
					-> ABMT	RP	27+	40+
P.L.	M/42	III A	L	large	F-MACHOP ->	RC	6+	/
					-> ABMT	RC	30+	36+
F.L.	M/63	III B	H	medium	CHOP	RP	3	24
N.L.	F/50	IV A	LI	mixed	CHOP	RC	2	15+
I.S.	M/68	IV A	LI	mixed	CHOP	N.R.	/	5
P.S.	M/77	IV A	H	large	F-MACHOP	N.R.	/	9
F.L.	M/66	IV B	H	mixed	CHOP	RP	1	10
C.R	M/32	IV A	L	medium	LAL 0288	RC	8	33
P.E.	M/69	IV B	H	medium	CHOP	RP	3	13+
M.G.	M/45	IV A	L	mixed	CHOP ->	RP	5	/
					-> BMT	RC	24+	28+
R.A.	M/55	IV A	HI	mixed	F-MACHOP	RP	6	11
C.P.	F/33	IV A	HI	medium	F-MACHOP	N.R.	/	14
C.G.	M/61	IV B	H	medium	MEV	N.R.	/	2
A.I.	M/39	IV B	HI	large	F-MACHOP	RC	2	7
P.G.	M/48	IV B	HI	mixed	ABVD	RC	7	17+
V.M.	F/54	IV A	L	medium	F-MACHOP->	RC	5+	/
					-> ABMT	RC	8+	20+
T.A.	M/57	IV B	HI	large	F-MACHOP ->	RP	7+	/
					-> ABMT	RC	8+	22+

Abbreviations. L: low; LI: low-intermediate; HI: high-intermediate; H: high; NE: not evaluable; CR: complete remission; PR partial remission; NR: resistant; PFS: progression-free survival; OS: overall survival; +: alive and in CR/PR; CHOP: cyclophosphamide, adriamycin, vincristine, prednisone; F -MACHOP: cyclophosphamide, adriamycin, vincristine, cytosine arabinoside, methotrexate, prednisone; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; MEV: methotrexate, cyclophosphamide, vincristine; LAL 0288: multiagent combination of vincristine, daunoblastine, prednisone, L-asparaginase, mitoxantrone, cytosine arabinoside, methotrexate, etoposide, vepeside; CVP: cyclophosphamide, vincristine, prednisone; BMT: allogeneic bone marrow transplantation; ABMT: autologous bone marrow transplantation.

high risk. The PFS (median 7 months) and OS (median 24 months) curves of high-intermediate + high risk patients were less favorable than the PFS and OS (in both cases the median has yet to be reached) of patients with low + low-intermediate risk (p=0.30 and p=0.08, respectively) (Figure 4).

Discussion

The prognosis of and therapeutic approach to peripheral T-cell lymphomas, unspecified, recently grouped in the REAL classification, are still not well defined. Being a heterogeneous group of diseases with respect to clinical presentation and behavior, in the past they were treated differently with chemotherapeutic regimens of varying intensities.

From a review of the literature (Table 4), there seems to be a general agreement in considering these lymphomas as relatively aggressive diseases;

Table 3. PTCL-U: response rate of 23 evaluable patients.

Classification system	No. patients	CR %	PR %	NR %
Ann Arbor stage				
II	4	50	50	0
III	5	60	40	0
IV	14	50	21	29
Cell size				
Large	7	72	14	14
Mixed	8	50	37.5	12.5
Medium	8	37.5	37.5	25
International Prognostic Index				
Low	8	75	25	0
Low-intermediate	2	50	0	50
High-intermediate	8	62.5	25	12.5
High	5	0	60	40
Treatment				
CHOP	9	22	67	11
F-MACHOP	9	34	44	22
ABVD	1	100	0	0
MEV	1	0	0	100
LAL 0288	2	100	0	0
CVP	1	100	0	0

CR: complete remission PR: partial remission NR: resistant.

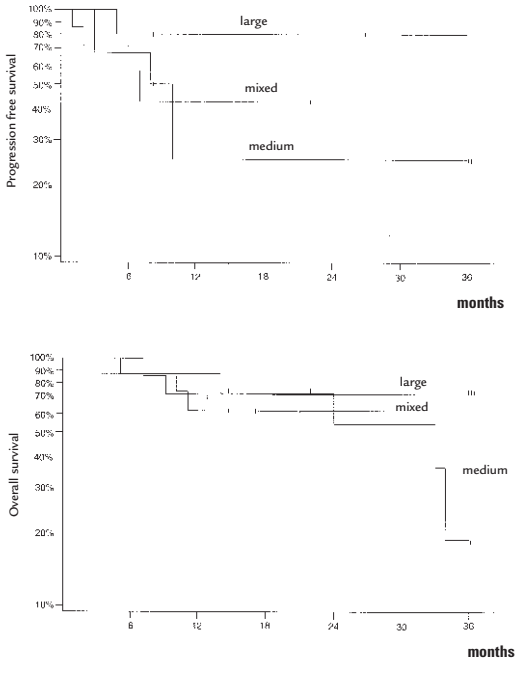

Figure 3. PTCL-U: 3-year PFS and OS according to cell size. The log-rank test of the 3 groups was not significant for PFS (p=0.38) or OS (p=0.59).

Table 4. PTCL: main literature data.

Study	Pts.	Histology	Median age (yrs)	M/F	Stage III-IV (%)	B symptoms (%)	Extranodal involvement	Treatment	Response rate (%)	Median OS (months)
Levine et al.[8], 1981	19	T-IBS	52	7/12	89	common	BM 46 %	MCC	CR 7	20
Brisbane et al.[9], 1982	9	PTCL*	59.8	5/4	77.7	55.5	/	MCC	CR 28 CR+PR 57	11
Cossman et al.,[10] 1984	25	PTCL*	/	10/5	87	83	/	MCC (ProMACE -MOPP 17/25)	CR 60 CR+PR 80	31
Greer et al.[11] 1984	42	PTCL*	63.5	33/11	79	67	frequent	MCC	CR 24	11
Grogan et al.[12] 1985	11	PTCL*	69	7/4	63.6	36	100 % (skin 54.5 %)	CHOP: others CR+PR 100	CR 50	9
Van der Walk et al.[13] 1986	10	PTCL*	63.6	5/5	70	/	80 % (skin 70 %)	MCC: others	CR 50 CR+PR 100	22
Horning et al.[14] 1986	41	PTCL**	56	22/19	68	27	frequent (skin 24 %)	MCC: others	/	29
Hanson et al.[15] 1986	30	PTCL*	61	20/10	80	84	BM 80 %	MCC: others	/	11
Weiss et al.[16] 1996	40	PTCL**	53	27/13	60	50	52 %	MCC	CR 52.5 CR+PR 65	variable due to histotype
Liang et al.[17] 1987	31	PTCL*	57	17/14	94	45	frequent (BM 41 %)	MCC	CR 48 CR+PR 65	13
Weisemburg et al.[18] 1988	42	PTCL*	60	21/21	62	55	52. %	MCC	CR 53	17
Lippman et al.[19] 1988	20	LC-PTCL	58.8	16/4	80	60	85 % (skin 85%)	MCC (Doxo)	CR 50 CR+PR 85	18
Cheng et al.[20] 1989	34	PTCL*	57	/	87	45	frequent (BM 35 %)	MCC: others	CR 62	21
Armitage et al.[21] 1989	134	PTCL*	57	79/55	72	57	frequent (BM 35 %)	MCC (CHOP 80/134)	CR 50	17
Chott et al.[22] 1990	75	PTCL**	54	35/40	72	57	20 %	MCC	CR 37	23
Coiffier et al.[23] 1990	108	PTCL**	/	/	77	39	/	MCC (Doxo)	CR 72 CR+PR 81	42
Stein et al.[24] 1990	17	LC-PTCL	49	12/5	64.7	59	47 %	MCC	/	11
Kwak et al.[25] 1991	21	LC-PTCL	/	10/11	71	29	30 %	MCC (Doxo)	CR 95	79% at 5 yrs
Montalbàn et al.[26] 1993	41	PTCL*	/	/	83	80	BM 34 %	/	CR 48 CR+PR 75.6	12
Siegert et al.[27] 1994	25	PTCL*	55	15/10	48	60	/	MCC (Doxo)	CR 64 CR+PR 88	69% at 2 yrs

*Abbreviations: IBS = immunoblastic; LC-PTCL = large cell PTCL; BM = bone marrow; MCC = multiagent combination chemotherapy; Doxo = containing doxorubicin; RT = radiotherapy; CR = complete remission; PR = partial remission; *cutaneous T-cell lymphomas excluded; **included T-CLL, angioimmunoblastic lymphomas, anaplastic large cell T-NHL.*

however, extremely variable results in the outcome of therapy are reported. The great variability of response to doxorubicin-containing regimens (i.e. CHOP), which were the ones most frequently used, could be explained either by the histological heterogeneity of PTCLs or by the inclusion in some retrospective studies of lymphomas with different aggressivness, such as angioimmunoblastic lymphoma, anaplastic T-cell lymphoma or T-cell chronic lymphocytic leukemia.[14,16,22,23]

In our study we retrospectively analyzed a very selected cohort of patients affected by PTCL-U, according to the REAL classification, with the aim of evaluating the clinico-hematological features at diagnosis, the relationship between the outcome and the Ann Arbor stage, cell size and type of treatment, and the relevance of the International Prognostic Index.

Similarly to that was previously described by other authors (Table 4), our study also found that the clinical presentation of PTCL-U is aggressive. The majority of our patients were elderly males with advanced stage and extranodal involvement, but no CNS localization, which has been rarely described[20,26] except by Kaufman *et al*.[28] In accordance with previous reports, Ann Arbor stage was correlated with outcome, even though its prognostic value was not highly significant. Patients in stage IV had a lower response rate (overall response 71%, CR 50%), lower median PFS and OS (6 and 33 months, respectively). Our experience indicated an apparently better prognosis (albeit without statistical significance) for patients with a large cell size pattern of infiltration. This result is in contrast with previous studies[15,17,21,23,26] in which cell size had no prognostic relevance, or at least a better outcome for small cell size histotypes was evidenced.[16,20] Of course, it must be borne in mind that in our analysis the number of

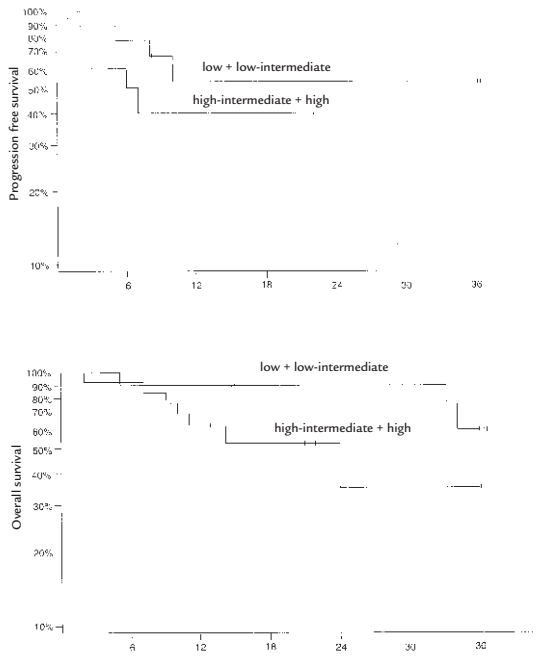

Figure 4. PTCL-U: 3-year PFS and OS according to the International Prognostic Index. The log-rank test of the 2 groups (low + low-intermediate and high-intermediate + high) was not significant for PFS (p=0.30) or OS (p=0.08).

cases in each group was rather small.

In our study we applied the International Prognostic Index, which is currently the most widely used prognostic classification system for high- and low-grade NHLs. Four risk groups were selected, but due to the small number of patients we considered only two different categories: low + low-intermediate and high-intermediate + high risk groups. A clear difference in the outcome of the two groups was observed, although it was not significant for the reasons previously mentioned. Our results suggest that the International Prognostic Index is a valid prognostic system for selecting poor risk patients with PTCL-U for whom the use of more aggressive therapeutic strategies is mandatory. In fact the therapeutic results obtained in these poor risk patients with conventional chemotherapy are very disappointing. No improvement in response rate, PFS and OS were achieved by using a third generation chemotherapeutic program (F-MACHOP) as compared to CHOP or other multiagent combination regimens.

New treatment strategies should therefore be developed and autologous or allogeneic BMT could play an important role in his setting. Vose *et al*.[29] reported on 17 patients who underwent autologous BMT for recurrent PTCLs, with a durable CR being achieved in 29% of the cases. Gordon *et al*.[30] successfully employed autologous and allogeneic BMT in 12 children and adolescents with PTCLs in second CR or in relapse. Other sporadic cases of PTCL which were transplanted have been reported together with other lymphomas, mainly of B-cell origin. In our experience, 5 poor risk patients (according to Ann Arbor stage) were auto- or allotransplanted, and they are alive and in complete remission. However, it must be considered that 3 of them fell into the low risk and 2 into the high risk group when they were stratified according to the International Prognostic Index.

In conclusion, PTCL-U are uncommon lymphomas mostly affecting adults, have aggressive clinical presentation and poor outcome. The International Prognostic Index is useful for stratifying patients into different prognostic risk groups. High-dose chemotherapy followed by autologous or allogeneic BMT could be employed in high-intermediate and high risk patients, whose life expectancy is quite similar to that of patients with acute leukemia.

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