The adjusted International Prognostic Index and β-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma

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ABSTRACT

Background and Objectives

Preliminary data on the use of autologous stem cell transplantation (ASCT) as a salvage therapy for peripheral T-cell lymphoma (PTCL) indicate that the results are similar to those obtained in aggressive B-cell lymphomas. The aim of our study was to analyze outcomes of a large series of patients with PTCL with a prolonged follow-up who received ASCT as salvage therapy.

Design and Methods

Between 1990 and 2004, 123 patients in this situation were registered in the GELTAMO database. The median age at transplantation was 43.5 years; in 91% of patients the disease was chemosensitive.

Results

Seventy-three percent of the patients achieved complete remission, 11% partial remission and the procedure failed in 16%. At a median follow-up of 61 months, the 5-year overall and progression-free survival rates were 45% and 34%, respectively. The presence of more than one factor of the adjusted International Prognostic Index (a-IPI) and a high β2-microglobulin at transplantation were identified as adverse prognostic factors for both overall and progression-free survival and allowed the population to be stratified into three distinct risk groups.

Interpretation and Conclusions

Our data show that approximately one third of patients with PTCL in the salvage setting may enjoy prolonged survival following ASCT, provided they are transplanted in a chemosensitive disease state. The a-IPI and β2-microglobulin level predict the outcome after ASCT in relapsing/refractory PTCL.

Key words: peripheral T-cell lymphoma, international prognostic index, β-2-microglobulin, autologous stem cell transplantation.

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Peripheral T-cell lymphoma (PTCL) is an heterogeneous group of lymphomas constituting the largest group of adult T-cell non-Hodgkin's lymphomas.[1] According to the WHO classification, PTCL account for approximately 10% of aggressive lymphomas, excluding cutaneous, lymphoblastic and human T-cell leukemia/lymphoma.[2] Unfortunately, there is little information concerning these heterogeneous entities, mainly due to their relatively low frequency and because they have usually been assessed as part of larger clinical studies on aggressive B-cell lymphomas. The T-cell immunophenotype is almost unanimously accepted as conferring a poor prognosis:[3-6] although in some reports this poor prognosis has been explained by a greater distribution of unfavorable prognostic factors,[7] the T-cell immunophenotype was considered as an independent unfavorable prognostic factor in most relevant series to date.[5,8] The 5-year survival of patients with most T-cell lymphomas is in the range of 20-40%, which is lower than that of patients with the corresponding aggressive B-cell lymphomas.[3]

Having established that high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCT) is currently the best available salvage therapy for patients with aggressive chemosensitive lymphomas,[9] it is logical to review whether this therapy offers benefits to patients with the corresponding aggressive T-cell lymphomas. Indeed, the majority of retrospective series showed a similar outcome between aggressive B- and T-cell lymphomas after ASCT[10-12] in the same setting, although the studies generally involved a small number of patients and a short follow-up period. Furthermore, little or no relevant information is available regarding prognostic factors in order to define which patients might benefit from this therapeutic modality and which will not.

In the present study, we analyze our experience with a large group of PTCL patients observed over a prolonged period. A major goal of our study was to investigate the importance of clinical covariates in order to obtain relevant pre-transplant prognostic information.

Design and Methods

Patients

Between 1990 and 2004, 123 patients were included in the GEL/TAMO registry with a diagnosis of PTCL according to the REAL or WHO classifications.[2,13] These patients were eligible to receive HDC/ASCT, if they had PTCL, excluding lymphoblastic or cutaneous lymphoma, which had relapsed or if they had failed to achieve complete remission after induction treatment. Patients with severe concomitant medical or psychiatric illnesses, central nervous system involvement or who were human immunodeficiency virus seropositive, were not eligible for this therapy. Other criteria for ineligibility included bilirubin levels above 1.5 mg/dL, a cardiac ejection fraction less than 50% and pulmonary function test and diffusing lung capacity less than 50% of predicted values. The pathologist in each center established the histological diagnosis. Those cases with difficult diagnostic features were referred to expert hematopathologists following the recommendations of the group. The histological subtypes were as follows: 57% PTCL unspecified (PTCL-u) (n=70), 25% anaplastic large T-cell lymphoma (n=31), 6% lymphoepithelioid T-cell lymphoma (n=7), 8% angioimmunoblastic T-cell lymphoma (n=10), 2% hepatosplenic γ/δ T-cell lymphoma (n=2), 2% subcutaneous panniculitis-like T-cell lymphoma (n=2) and 1% intestinal T-cell lymphoma (n=1). The disease stage was evaluated according to the Ann Arbor staging system and patients were staged according to standard procedures following physical examination, blood and serum assays, chest X-rays, and computed tomography of the neck, chest, abdomen and pelvis. Bone marrow aspirates and biopsies were obtained prior to HDC, and other staging procedures were performed at diagnosis to fully determine the pretransplant state. Standard variables of the adjusted International Prognostic Index (a-IPI) (lactate dehydrogenase [LDH], performance status and Ann Arbor stage)[7] and other variables of known prognostic importance in this type of lymphomas were evaluated, such as M.D. Anderson tumor score (Ann Arbor stage, LDH, β2-microglobulin, B-symptoms and bulky disease) and the Prognostic Index for PTCL (PIT) (age, LDH, bone marrow involvement and performance status).[14,15] The clinical characteristics of the patients at diagnosis and at the moment of transplantation are reported in Table 1.

Table 1. Clinical characteristics of patients at diagnosis and at transplantation.

Variable	*At diagnosis*	*At transplantation*
Age		43,5 (14-72)
Sex (male/female)	78 (63%)/45 (37%)	
Ann Arbor Stage III-IV	89 (72%)	43 (35%)
B-symptoms	53 (43%)	11 (9%)
>1 extranodal sites	30 (25%)	7 (6%)
BM involvement	27 (22%)	12 (10%)
Bulky disease	30 (25%)	3 (2%)
ECOG > 1	37 (31%)	9 (7%)
High LDH	54 (47%)	22 (18%)
High β2M	31 (38%)	36 (41%)
Adjusted IPI 2-3	54 (47%)	20 (16%)
Tumor score 3-5	47 (45%)	11 (9%)
Pretransplant regimens		
CHOP	74 (60%)	
Others anthracycline-based	49 (40%)	
Treatment lines pretransplant		
One line	54 (44%)	
Two lines	63 (51%)	
Three lines	6 (5%)	

Table 2. Transplant-related factors.

Median months to transplant (range)	*12 (3-215)*
Disease status	
First PR	44 (36%)
Second or more CR	44 (36%)
Second or more PR	20 (16%)
Refractory	11 (9%)
Non-treated relapse	4 (3%)
Conditioning regimens	
BEAM	57 (46%)
BEAC	34 (28%)
Cy plus TBI	13 (11%)
CVB	12 (10%)
Others	7 (6%)
Stem cell source	
BM	89 (72%)
PB	27 (22%)
BM plus PB	7 (6%)
Median aphereses (range)	2 (1-7)
Mobilization growth factor	91/96 (95%)
Purging	5 (4%)
Cytokines postransplant	
G-CSF	82 (67%)
GM-CSF	6 (5%)
None	34 (28%)
Treatment-related mortality	5 (4%)
Engraftment	118/118 (100%)

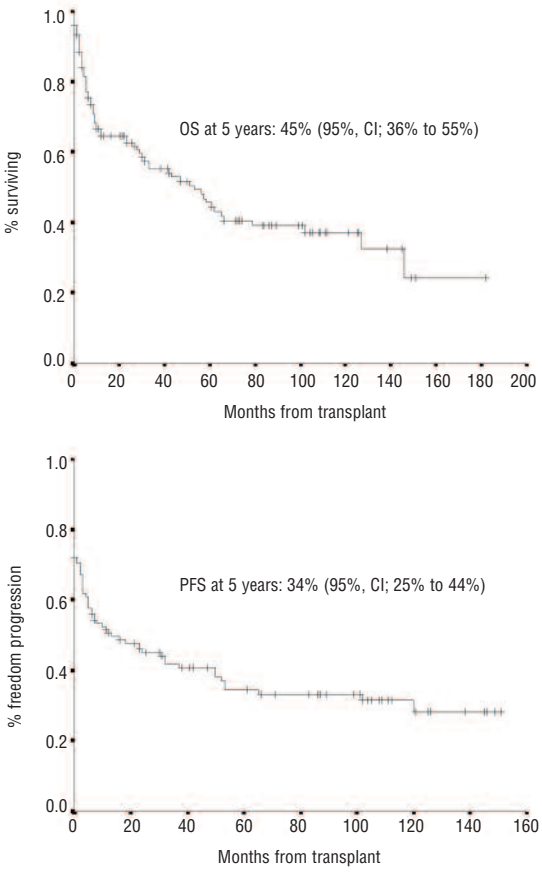

Figure 1. Overall and progression-free survival.

Treatment plan

The pretransplant regimes followed were not uniform, but they were mainly based on anthracycline-containing regimes (Table 1). The preparative regimes and other transplant-related factors are presented in Table 2. Of the 123 patients, 57 patients received the BEAM regime (46%); 34 BEAC (28%); 13 cyclophosphamide/total body irradiation (11%); and the remaining 19 other regimes (15%). The source of stem cells was mobilized peripheral blood (PB) in 89 patients (72%), bone marrow in 27 (22%) and from both in 7 patients (6%). Among the 96 patients who received PB stem cells, the stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF) in 34 (35%), with G-CSF and chemotherapy in 57 (59%), and with chemotherapy alone in five cases.

Response and follow-up criteria

The response to therapy was evaluated by the investigator responsible in each center at 1, 3 and 6 months post-ransplantation and every 6 months thereafter. Evaluations were carried out following standard guidelines[16] and included physical examination, complete blood counts, serum biochemistry, bone marrow aspiration and biopsy, and radiological studies as mentioned above. A complete response (CR) was defined as the disappearance of all clinical evidence of lymphoma for a minimum of 4 weeks, with no persisting disease related symptoms. Prior to transplantation, a complete restaging was performed in all patients. A partial response (PR) was defined as a decrease greater than 50% in the sum of the products of the two longest diameters of all measurable lesions for at least 4 weeks and non-measurable lesions had to decrease by at least 50%. In this category no increase in lesion size and no new lesions were tolerated. Progressive disease (PD) was defined as any increase greater than 25% in the sum of the diameter of any measurable lesions or the appearance of new lesions. Stable disease (SD) was considered as any condition intermediate between PR and PD. Transplant-related mortality (TRM) was defined as death within 100 days after HDC/ASCT that was unrelated to the disease, relapse or progression. Toxic mortality was considered at any time if it was related to the procedure.

Statistical methods

Overall survival (OS) and progression-free survival (PFS) were measured from the date of transplantation and were estimated according to the Kaplan-Meier method.[17] Comparisons among those variables of interest were performed by the log-rank test.[18] Multivariate analysis with the variables that proved to be significant in univariate analysis was performed according to the Cox proportional hazard regression model.[19] All p-values reported were two-sided and statistical significance was defined at $p<0.05$.

Results

Outcome

Response to transplantation was as follows: 87 of the 119 (73%) patients in whom response could be assessed achieved a CR, 13 a PR (11%) and the transplant failed to produce benefits in 19 patients (16%) who had SD or PD. The post-transplantation response was not evaluated in four patients who died of transplant-related causes: these patients were excluded from PFS and disease-free survival (DFS) analyses. After a median follow-up for the surviving patients of 61 months (range, 0-182), 57 (46%) were still alive. Indeed, the OS at 5 years was 45% (95% CI; 36% to 55%) while the PFS was 34% (95% CI; 25% to 44%) (Figure 1). Moreover, the DFS at 5 years for complete responders was 47% (95% CI; 35% to 58%). Most of the patients who died did so due to progression of the disease (n=53), although three patients died of a second neoplasia (malignancies in the lung, ovarian and uterus). No cases of myelodysplastic syndromes were observed during this follow-up period. The transplant-related mortality was 4%, with two cases of severe bleeding and three cases of fatal pneumonia.

Prognostic factors for OS and PFS

The univariate analysis of prognostic factors that might influence the OS and PFS is presented in Table 3. When we analyzed the influence of the pre-transplant status of the disease on the outcome, we found no differences between patients in second or subsequent CR (OS and PFS of 57% and 35%, respectively) or those transplanted in the first PR (OS and PFS of 50% and 47%, respectively). However, the outcome was significantly worse for those patients transplanted in the second or subsequent PR (OS and PFS of 33% and 23%, respectively) and those patients transplanted in the refractory state of the disease (OS and PFS of 9% and 10%).

We also identified the following factors at transplant that were associated with a poor OS (Table 3): more than one point in the ECOG performance status score, presence of B symptoms, more than one extranodal site of disease, high LDH and high β2-microglobulin. Among the prognostic systems analyzed, patients fared significantly worse when they had, at the time of transplantation, more than one factor of the a-IPI; more than two factors of the MD Anderson Tumor Score, or more than one factor of the PIT. Similarly, with respect to the PFS the factors associated with a poor outcome were the same as those that influenced OS with the exception of the presence of more than one extranodal site of disease and more than one point of the ECOG performance status score, which proved not to be significant factors. The aforementioned prognostic scores also influenced the PFS, as shown in Table 3.

Interestingly, patients who received radiotherapy after their transplant (n=17) had a better OS and PFS than patients who did not receive this consolidation therapy. However, this is a retrospective finding that should be confirmed in a prospective clinical trial, as there was no homogeneous protocol to define when radiotherapy should be administered post-transplantation. Among these patients, most had a *bulky* disease at diagnosis (11 of 17) and all but one received first-line consolidation (9 cases of PR and 1 with treatment failure) with HDC/ASCT followed by post-transplantation involved-field radiotherapy.

The group of patients with anaplastic T-cell lymphoma was analyzed separately since this group of patients has a more favorable prognosis if the tumor cells express the ALK tyrosine kinase. Unfortunately, information regarding this marker was not available for most of our patients. Nevertheless, we did not find any differences in response rate, OS or PFS between patients with anaplastic T-cell lymphoma and those with the other subtypes. In fact, the CR rate after transplant was 68% for the anaplastic group compared to 72% for the other non-anaplastic group. Similarly, the OS of both groups were 37% vs 48% (p=0.59), and the corresponding PFS were 29% and 36% (p=0.76), respectively.

Multivariate analysis

Following a multivariate analysis (Table 4), three factors emerged that provided significant independent information regarding the OS: more than one adverse factor of the a-IPI, a high β2-microglobulin level and more than one extranodal site of disease. In the case of PFS only β2-microglobulin remained independent. Thus, taking into account the clinical factors that were associated with both OS and PFS (β2-microglobulin and a-IPI, excluding more than one extranodal site) (Table 3), we analyzed the population with information regarding these two variables (n=88). As shown in Figure 2, this population could be divided into three distinct prognostic groups by this two widely used variables. Hence, patients with no pretransplant adverse factors (52% of the population) had an OS and PFS at 5 years of 60% and 43%, respectively. However, among patients who displayed one adverse factor (39% of the population), OS was 28% and PFS 24%. Notably, the patients in whom both factors were recorded pretransplant (9%) died of their disease. As all of them were transplanted as a first line therapy (six cases of 1st PR and two cases of 1st PD), these variables could be helpful for identifying patients whose disease state is refractory to both conventional and high-dose chemotherapy.

Table 3. Univariate analysis of prognostic factors at ASCT that influenced survival

Parameter	*N.*	*OS at 5 years (95% CI)*	*p*	*N.*	*PFS at 5 years (95% CI)*	*p*
Status at transplant			0.003			0.012
Second or more CR	44	57% (40-73)		44	35% (19-51)	
First PR	44	50% (33-66)		41	47% (32-63)	
Second or more PR	20	33% (8-58)		20	23% (4-42)	
First SD or PD	8	12% (0-35)		7	14% (0-40)	
Second or more SD or PD	3	0%		3	0%	
Non treated relapse	4	37% (0-94)		4	0%	
ECOG PS			<0.001			0.079
0 or 1	114	49% (38-59)		112	36% (26-46)	
2 to 4	9	11% (0-31)		7	14% (0-40)	
Ann Arbor stage			0.077			0.07
I or II	80	53% (41-65)		79	38% (26-50)	
III or IV	43	31% (16-47)		40	27% (13-41)	
B symptoms			0.006			0.034
No	112	48% (37-58)		109	36% (26-45)	
Yes	11	20% (0-46)		10	20% (0-45)	
N. of extranodal sites			0.009			
0 or 1	116	48% (38-58)		113	35% (25-44)	0.7
More than 1	7	14% (0-40)		6	33% (0-71)	
BM involvement			0.93			0.7
Not involved	111	46% (36-57)		107	33% (23-43)	
Involved	12	42% (14-70)		12	42% (14-70)	
Bulky disease			0.4			0.95
No	120	45% (35-55)		116	34 (25-44)	
Yes	3	67% (13-100)		3	33 (0-87)	
LDH			<0.001			0.034
Normal	101	50% (39-61)		100	36% (25-46)	
High	22	24% (6-42)		19	26% (6-46)	
β2-microglobulin			<0.001			0.002
Normal	52	58% (43-73)		50	44% (29-58)	
High	36	17% (3-32)		34	15% (2-28)	
a-IPI			<0.001			0.001
0 or 1	103	53% (42-64)	n=123	102	38% (28-48)	
More than 1	20	11% (0-24)		17	12% (0-27)	
TS			<0.001			<0.001
0 to 2	108	50% (39-60)		105	37% (27-47)	
3 to 5	11	9% (0-26)		10	10% (0-29)	
PIT			<0.001			0.044
0 or 1	109	48% (38-59)		107	35% (26-45)	
More than 1	11	18% (0-41)		9	22% (0-49)	
RT post-ASCT			0.020			0.005
Yes	17	69% (47-92)		17	63% (39-87)	
No	106	41% (30-52)		102	29% (20-39)	

CR: complete response; PR: partial response; PD: progressive disease; ECOG PS: Eastern cooperative group performance status; BM: bone marrow; a-IPI: adjusted-International Prognostic Index; TS: MD Anderson tumor score; PIT: prognostic index for peripheral T-cell lymphoma; RT post-ASCT: radiotherapy after autologous stem cell transplantation.

Discussion

The results obtained with ASCT as a salvage therapy and with a long follow-up confirm preliminary data obtained both by ourselves and others.[10–12,20–22] Indeed, the current report of 123 patients with a prolonged median observation time of 61 months confirms our previously published results involving 78 patients transplanted in the context of salvage therapy. In that series of patients, we reported an OS and PFS of 45% and 39%, respectively, after 37 months of follow-up.[22] No differences in outcome can be seen when comparing these results with those obtained in patients with aggressive B-cell lymphomas.[23] Similarly, a 58% OS and 48% PFS was reported in a study of 40 patients, 50% of

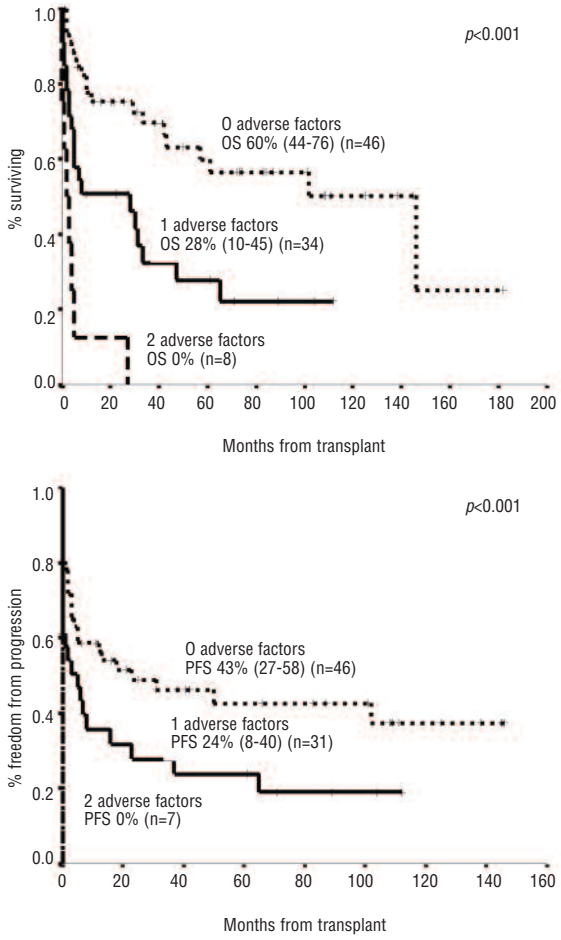

Figure 2. OS and PFS at 5 years according to the pre-transplantation a-IPI and β2-microglobulin status.

Table 4. Multivariate analysis of prognostic factors influencing the OS and PFS.

Parameter	Overall survival (n=86) p	RR (exp. B)	95% CI	Progression-free survival (n=84) p	RR (exp. B)	95% CI
a-IPI > 1	0.017	2.41	1.17-4.94	0.11	1.82	0.87-3.81
High B2M	<0.001	3.07	1.68-5.59	0.008	2.08	1.21-3.57
>1 extranodal site	<0.001	8.02	2.78-23.1	–	–	–
B-symptoms	0.36	1.88	0.48-7.29	0.91	1.08	0.31-3.80
High LDH	0.28	0.47	0.12-1.83	0.33	0.53	0.15-1.92
TS > 2	0.79	0.79	0.13-4.69	0.28	2.85	0.42-19.18
PIT > 1	0.94	1.06	0.26-4.27	0.62	0.69	0.16-3.00
RT post-ASCT	0.13	0.44	0.15-1.26	0.07	0.41	0.15-1.08
Status at transplant	0.95	–	–	0.64	–	–
ECOG PS > 1	0.68	1.50	0.21-10.48	–	–	–

RR: relative risk; CI: confidence interval; a-IPI: adjusted-International Prognostic Index; β2M: β2-microglobulin; LDH: lactate dehydrogenase; TS: tumor score; PIT: Prognostic Index for PTCL; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

whom had PTCL-u.[12] Moreover, in another study of 21 patients who underwent ASCT as salvage therapy for relapsing and refractory disease, the 4-year OS rate was 34%.[11] However, most reported series involve a small number of patients and have a short follow-up; our series of 123 patients with a median follow-up of more than 5 years enables more meaningful conclusions to be drawn.

Interestingly, we do not observe significant differences in the outcome between patients with anaplastic T-cell lymphoma and PTCL-u when ASCT is used in the salvage setting. Patients with anaplastic T-cell lymphoma expressing ALK have been shown to display very favorable responses when treated with ASCT, either as a front-line therapy or as salvage therapy.[8,24-26] Thus, the fact that we could not find differences between this group of patients and the rest of the patients may indicate that ASCT overcomes the unfavorable prognosis of the non-anaplastic group in the salvage setting or alternatively, that most of the anaplastic T-cell lymphoma patients in our population do not express ALK. Unfortunately, data regarding the ALK marker were not available for this group of patients. Nevertheless, how anaplastic T-cell lymphomas that express ALK and those that do not express ALK respond to ASCT should be specifically addressed, to determine whether they behave similarly to other subtypes of PTCL in the salvage setting.

In our multivariate analysis, only single variables emerged as significant factors that influenced OS and PFS at the univariate level. In fact, patients who had more than one adverse factor of the a-IPI pre-transplantation and elevated β2-microglobulin responded poorly to this therapeutic modality. The IPI serves to classify patients with aggressive lymphomas into different risk groups[7] and indeed, it has also been shown to have prognostic value for patients with PTCL.[5,27] On the other hand, elevated β2-microglobulin is known to be an adverse prognostic factor in lymphoproliferative diseases, being directly related to malignant tumor burden[28] but also maintains its adverse prognostic role when other causes, such as renal impairment, are the origin of the raised levels.[14] Although this factor is not included in the IPI, there is strong evidence of its independent prognostic value in aggressive non-Hodgkin lymphomas.[14]

We, therefore, reasoned that these two variables might be useful to divide the population into different groups, enabling us to predict the benefit of ASCT to patients prior to performing the transplant. In fact, of the 88 informative cases, 46 patients (52%) did not have either of these two factors at the time of transplantation and remarkably these patients had a 60% probability of being alive 5 years after transplantation. This figure contrasts with the 28% probability of survival for the population that had one of these factors at the time of transplantation. Furthermore, none of the 8% of the population that had both factors at transplantation were alive after 5 years. We consider that if these results are con-

firmed in an independent population, these two variables could prove to be reliable and user-friendly prognostic indicator. Moreover, the system allowed us to identify a small group of patients prior to transplantation who did not benefit from this procedure, in addition to the well-known chemoresistant cases. In fact, new, experimental treatments should be evaluated for salvage therapy of patients who are not chemosensitive or who display both of these adverse factors. Among such innovative approaches, non-myeloablative allogeneic hematopoietic transplantation has been tested. Although this therapy has produced excellent preliminary results, these must be confirmed.[29] New drugs, such as histone deacetylase inhibitors (HDAI), bortezomib and rapamycin analogs, as well as monoclonal antibodies that specifically target T-cell markers, are also being tested.[30-33] Indeed, given that adriamycin offers little benefit to patients with T-cell lymphomas,[34] the search should continue for drugs that are active against T-cell lymphomas and that provide a more specific approach to treat this group of lymphomas.

Our data confirm that the results with ASCT in both aggressive T- and B-cell lymphomas are similar in the relapse setting over a long observation period. Therefore, it is logical to consider that front-line ASCT consolidation of poor prognosis PTCL might improve the outcome of this condition. Given the relatively low frequency of PTCL, prospective studies and specifically randomized studies are unlikely to be feasible outside of an international setting, although preliminary results of some studies have been presented.[35-40] Many questions urgently need to be answered. For instance, the biological, prognostic and therapeutic implications of data from tissue arrays and genomic cluster analysis of the different so-called PTCL must be addressed, as has been done for aggressive B-cell lymphomas.

This task will be hampered by the fact that PTCL comprise a heterogeneous group of rare entities that probably have major differences.

In conclusion, our data show that approximately one third of patients with PTCL treated with ASCT in the salvage setting may enjoy a prolonged survival, provided they are transplanted in a chemosensitive disease state. The use of a-IPI and β2-microglobulin pre-transplantation enables us to divide the population into three very distinct prognostic groups, thus providing relevant information that may aid therapeutic decisions. In fact, patients in a refractory state pre-transplantation or who have the two adverse factors considered do not appear to benefit from ASCT, indicating that such patients need innovative treatment. Finally, taking into account the dismal prognosis of these patients when given conventional chemotherapy alone as a front-line treatment, these results in the salvage setting suggest that consolidation with ASCT as a front-line therapy should be tested.

Authors' Contributions

JR, AG and MDC were responsible of conception and design, analysis and interpretation, drafting the paper and final approval; EC, JJL, RA, AS, JZ, AFS, MB, CS, AL and MRV were responsible for drafting and revising critically the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

References

1. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997;89:3909-18.
2. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361-92.
3. Armitage JO, Vose JM, Linder J, Weisenburger D, Harrington D, Casey J, et al. Clinical significance of immunophenotype in diffuse aggressive non-Hodgkin's lymphoma. J Clin Oncol 1989;7:1783-90.
4. Coiffier B, Brousse N, Peuchmaur M, Berger F, Gisselbrecht C, Bryon PA, et al. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. The GELA (Groupe d'Etude des Lymphomes Agressives). Ann Oncol 1990;1:45-50.
5. Melnyk A, Rodriguez A, Pugh WC, Cabannillas F. Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. Blood 1997; 89:4514-20.
6. Morabito F, Gallamini A, Stelitano C, Callea V, Guglielmi C, Neri S, et al. Clinical relevance of immunophenotype in a retrospective comparative study of 297 peripheral T-cell lymphomas, unspecified, and 496 diffuse large B-cell lymphomas: experience of the Intergruppo Italiano Linformi. Cancer 2004;101:1601-8.
7. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-94.
8. Gisselbrecht C, Gaulard P, Lepage E, Coiffier B, Briere J, Haioun C, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998;92:76-82.
9. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-5.
10. Rodriguez J, Munsell M, Yazji S, Hagemeister FB, Younes A, Andersson B, et al. Impact of high-dose chemotherapy on peripheral T-cell lymphomas. J Clin Oncol 2001; 19: 3766-70.
11. Kewalramani T, Nimer S, Zelenetz A, Hamlin P, Horwitz S, Qin J, et al. Similar outcomes for chemosensitive (CS) relapsed or primary refractory peripheral T-cell lymphoma (PTCL) and diffuse large B-cell lymphoma (DLBCL) treated with autologous transplantation (ASCT). Blood 2002; 100:646a[abstract].
12. Blystad AK, Enblad G, Kvaloy S, Berglund A, Delabie J, Holte H, et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. Bone Marrow Transplant 2001; 27:711-6.
13. World Health Organization Classifi-

cation of Tumours. Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues. Lyon: IARC Press. 2001.
14. Rodriguez J, Cabanillas F, McLaughlin P, Swan F, Rodriguez M, Hagemeister F, et al. A proposal for a simple staging system for intermediate grade lymphoma and immunoblastic lymphoma based on the 'tumor score'. Ann Oncol 1992; 3:711-7.
15. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004; 103:2474-9.
16. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
17. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-81.
18. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 1977;35:1-39.
19. Cox DR. Regression models and life-tables. J R Stat Soc 1972;34:187.
20. Rodriguez J, Caballero MD, Solano C, Lahuerta JJ, Arranz R, Sureda A, et al. High-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) in patients with primary refractory aggressive non-Hodgkin's lymphoma. Bone Marrow Transplant 2001;27[Suppl 1]:P668.
21. Rodriguez J, Caballero MD, Gutierrez A, Marin J, Lahuerta JJ, Sureda A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol 2003; 14:1768-75.
22. Rodriguez J, Caballero MD, Gutierrez A, Gandarillas M, Sierra J, Lopez-Guillermo A, et al. High dose 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;88:1372-7.
23. Caballero MD, Perez-Simon JA, Iriondo A, Lahuerta JJ, Sierra J, Marin J, et al. High-dose therapy in diffuse large cell lymphoma: results and prognostic factors in 452 patients from the GEL-TAMO Spanish Cooperative Group. Ann Oncol 2003;14:140-51.
24. Tilly H, Gaulard P, Lepage E, Dumontet C, Diebold J, Plantier I, et al. Primary anaplastic large-cell lymphoma in adults: clinical presentation, immunophenotype, and outcome. Blood 1997;90:3727-34.
25. Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913-21.
26. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C, et al. ALK+ lymphoma: clinicopathological findings and outcome. Blood 1999;93:2697-706.
27. Lee HK, Wilder RB, Jones D, Ha CS, Pro B, Rodriguez MA, et al. Outcomes using doxorubicin-based chemotherapy with or without radiotherapy for early-stage peripheral T-cell lymphomas. Leuk Lymphoma 2002;43:1769-75.
28. Hagberg H, Killander A, Simonsson B. Serum b2-microglobulin in malignant lymphoma. Cancer 1983; 51: 2220-5.
29. Corradini P, Dodero A, Zallio F, Caracciolo D, Casini M, Bregni M, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 2004;22:2172-6.
30. Orlowski RZ, Voorhees PM, Garcia RA, Hall MD, Kudrik FJ, Allred T, et al. Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. Blood 2005;105:3058-65.
31. Jundt F, Raetzel N, Muller C, Calkhoven CF, Kley K, Mathas S, et al. A rapamycin derivative (everolimus) controls proliferation through down-regulation of truncated CCAAT enhancer binding protein {b} and NF-{k}B activity in Hodgkin's and anaplastic large cell lymphomas. Blood 2005;106:1801-7.
32. Enblad G, Hagberg H, Erlanson M, Lundin J, MacDonald AP, Repp R, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004; 103:2920-4.
33. Talpur R, Apisarnthanarax N, Ward S, Duvic M. Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). Leuk Lymphoma 2002;43:121-6.
34. Vose J. International peripheral T-cell lymphoma (PTCL) clinical and pathologic review project: poor outcome by prognostic indices and lack of efficacy with anthracyclines. Blood 2005;106:811.
35. Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, 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;20:1533-8.
36. Reimer P, Ruediger T, Schertlin T, Geissinger E, Weissinger F, Einsele H, et al. Autologous stem cell transplantation as first-line therapy in peripheral T-cell lymphomas. A Prospective Multicenter Study. Blood 2005; 106:2074.
37. Lopez-Guillermo A, Mercadal S, Briones J, Xicoy B, Pedro C, Escoda L, 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;106:2077.
38. Cortelazzo S, Tarella C, Dodero A, Gianni AM, Francesco Z, Zanni M, et al. Long-term follow-up of high-dose chemotherapy followed by autologous stem cell transplantation in peripheral T-cell lymphomas at diagnosis. Blood 2004;104:909.
39. D´Amore F. High-dose therapy and autologous stem cell transplant as first line treatment in peripheral T-cell lymphomas. Ann Oncol 2005; 16:v15-v26.
40. Rodriguez J, Conde E, Gutierrez A, Arranz R, Leon A, Marin J, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. Eur J Haematol 2007;in press.