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

JOSÉ RODRIGUEZ, MARIA DOLORES CABALLERO, ANTONIO GUTIERREZ, MARCO GANDARILLAS, JORGE SIERRA, ARMANDO LOPEZ-GUILLERMO, ANNA SUREDA, JAVIER ZUAZU, JESUS MARIN, REYES ARRANZ, ENRIC CARRERAS, ANGEL LEON, ALBERTO FERNÁNDEZ DE SEVILLA, JESUS F. SAN MIGUEL, EULOGIO CONDE FOR THE GEL/TAMO SPANISH GROUP

Background and Objectives. Patients with aggressive non-Hodgkin's lymphomas (NHL) who do not obtain a complete response (CR) after induction chemotherapy have a poor prognosis. However, provided they are sensitive to the first regimen of chemotherapy, 25-40% of them with a B-cell phenotype may achieve long-term survival when treated with high dose chemotherapy and autologous stem cell transplantation (HDC/ASCT). The aim of this study was to analyze the efficacy of this therapy in the corresponding patients with peripheral T-cell lymphoma (PTCL).

Design and Methods. We retrospectively evaluated the efficacy of ASCT in 35 patients with PTCL from the GEL-TAMO registry, who did not achieve a CR to standard induction chemotherapy regimens for aggressive NHL. Thirty-one patients underwent transplantation after achieving a partial response (PR) and 4 patients were non-responders.

Results. Following HDC/ASCT, 23 (66%) of the patients achieved a CR, 4 (11%) a PR and in 7 (20%) cases the transplant failed. One patient was not evaluated because of early toxic death. With a median follow-up of the survivors of 37.5 months, 18 patients (51%) are alive and 15 patients (43%) are free of disease. Transplant-related mortality rate at 100 days was 11% and at 5 years the probabilities of survival, freedom from progression and disease-free survival for complete responders were 37%, 36% and 55% respectively. Pre-transplant lactate-dehydrogenase level, age-adjusted International Prognostic Index (aa-IPI) and tumor score correlated with survival.

Interpretation and Conclusions. One third of the patients with PTCL who fail to achieve CR to the first chemotherapeutic regimen can be rescued with HDC/ASCT. Pre-transplant values of IPI and tumor score risk systems for aggressive lymphomas were useful to predict subsequent survival.

Key words: autologous stem cell transplantation, T-cell lymphoma.

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From the Servicios de Hematología Hospital Universitario Son Dureta, Palma de Mallorca (JR, AG); Hospital Clínico Universitario, Salamanca (MDC, JSM); Hospital Marqués de Valdecilla, Santander (MG, EC); Hospital de la Santa Creu i Sant Pau, Barcelona (JS, AS); Hospital Clinic i Provincial, Barcelona (ALG, EC); Hospital de la Vall de Hebron, Barcelona (JZ); Hospital Nuestra Señora de Aranzazu, San Sebastian (JM); Hospital de la Princesa, Madrid (RA); Hospital General de Jerez, Jerez de la Frontera (AL); Institut Catala d'Oncologia, Barcelona, Spain (AFdS).

Correspondence: Dr. José Rodríguez, Servicio de Hematología, Hospital Universitario Son Dureta, Av/Andrea Doria 55, Palma de Mallorca 07014, Spain. E-mail: jrodriguez@hsd.es

In adult patients, the majority of aggressive T-cell non-Hodgkin's lymphomas (NHL) are peripheral T-cell lymphomas (PTCL).[1] Indeed, excluding cutaneous, lymphoblastic and adult T-cell leukemia/lymphoma, PTCL constitute approximately 10% of NHL.[2] No standard therapy has been established to treat this type of lymphoma and usually,[3-5] but not in all cases,[6,7] when standard therapeutic regimens for aggressive lymphomas are applied, the T-cell immunophenotype confers a poor prognosis. However, results of salvage therapies including high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT) seem to be similar to those observed for the corresponding B-cell immunophenotype.[8-10]

Failure to respond to induction therapy is defined as not achieving a complete response (CR) to the first-line therapy and represents a therapeutic challenge. Data from corresponding B-cell lymphomas indicate that approximately 40% of these patients can be salvaged with HDC/ASCT.[8,10,11] However, the efficacy of this therapy in patients with PTCL in whom induction has failed is less well defined. Recently, Kewalramani *et al*. reported that patients with primary refractory PTCL treated with HDC/ASCT respond in a similar manner to those with a corresponding primary refractory aggressive B-cell lymphoma.[9] To investigate this possibility further, we analyzed GEL-TAMO co-operative group patients with PTCL who had not achieved a complete response after induction chemotherapy and who then underwent HDC/ASCT as a salvage therapy. Our data suggest that patients with this type of lymphoma who fail to respond to induction therapy, do indeed fare similarly to patients with the corresponding aggressive B-cell lymphoma when treated with HDC/ASCT.

Design and Methods

Patients

Between July 1990 and December 1999, the hospitals participating in the Spanish Group for Lymphoma and Autologous Transplantation (GEL-TAMO) treated 115 PTCL patients with HDC/ASCT. In this report we retrospectively selected the 35 (30%) patients from the registry who had failed to respond to first-line induction treatment and who received HDC/ASCT as part of their salvage treatment. The clinical characteristics of the patients at diagnosis and at the time of transplantation are set out in Table 1. Briefly, at diagnosis 47% of the patients had an age-adjusted IPI (aa-IPI) score of 2 or 3. The maximal response to induction therapy in most

Table 1. Clinical characteristics.

Variable	*At diagnosis*	*At transplant*
Sex (M/F)	20 (57%)	15 (43%)
Median age (range)	44 (14-65)	
Ann Arbor Stage		
I-II	5 (14%)	18 (51%)
III-IV	30 (86%)	17 (49%)
B-symptoms	11 (31%)	3 (9%)
Number of extranodal sites		
0	12 (34%)	20 (57%)
1	12 (34%)	12 (34%)
>1	11 (32%)	3 (9%)
BM involvement	8 (23%)	5 (14%)
Bulky disease	11 (31%)	1 (3%)
ECOG > 1	10 (29%)	3 (9%)
High LDH	17 (51%)	10 (29%)
High β2M	10 (45%)	9 (45%)
Adjusted IPI		
0-1	17 (53%)	25 (73%)
2-3	15 (47%)	9 (27%)
NA	3	1
Tumor score		
0-2	15 (50%)	27 (84%)
3-5	15 (50%)	5 (16%)
NA	5	3
Pre-transplant regimens		
CHOP	22 (63%)	
MegaCHOP	3 (9%)	– –
Other	29%	

BM, bone marrow; LDH, lactate dehydrogenase; β2M, β2-microglobulin; NA, not available; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone.

Table 2. Transplant-related factors.

Treatment characteristics	
Disease status	
Partial response	31 (89%)
Refractory	4 (11%)
Conditioning regimens	
Cyclophosphamide plus TBI	6 (17%)
BEAM	10 (29%)
BEAC	13 (37%)
CVB	2 (6%)
Others	4 (11%)
Stem cell source	
BM	10 (29%)
PB	22 (63%)
BM plus PB	3 (9%)
Median apheresis (range)	2 (1-6)
Mobilization growth factor	92%
Purging	2 (6%)
Cytokines post-transplant	
G-CSF	21 (60%)
GM-CSF	4 (11%)
None	10 (29%)
Treatment-related mortality	4 (11%)
Engraftment	35 (100%)

TBI: total-body irradiation; BEAM: carmustine, etoposide, cytarabine, melphalan; BEAC: carmustine, etoposide, cytarabine, cyclophosphamide; CVB: carmustine, etoposide, cyclophosphamide; BM: bone marrow; PB: peripheral blood; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.

patients [(31/35) (89%)] was only partial although 4/35 (11%) were refractory or the disease progressed during treatment. At the time of transplantation, 43% of the patients had extranodal disease (14% bone marrow involvement). Most patients (91%) had an ECOG performance status of 0-1 and 3% of the patients had one or more bulky masses. High levels of β2-microglobulin and lactate dehydrogenase (LDH) were detected in 45% and 29% of the patients, respectively.

Therapy

The first-line and conditioning regimens for transplantation are presented in Table 2. All patients received standard induction regimens for aggressive NHL (22 patients CHOP, 3 MegaCHOP, 6 patients MACOP-B and 3 patients ProMACE-CYTABOM). A patient initially misdiagnosed with Hodgkin's disease received treatment with ABVD and 2 patients received radiotherapy pretransplantation. The median time from diagnosis to transplantation was 7 months and the conditioning regimens were based on BEAM or BEAC in 23 cases, total body irradiation/cyclophosphamide in 6 and other regimens in 6 patients.

Response assessment and follow-up criteria

The response to therapy was evaluated 1, 3 and 6 months after transplantation and, thereafter, every 6 months by the investigator responsible in each center. Evaluation followed the standard guidelines laid out by Cheson *et al.*[12] Complete response (CR) was defined as the disappearance of

all clinical evidence of lymphoma for a minimum of 4 weeks, with no persisting symptoms related to the disease. Prior to transplantation a complete restaging was performed in all patients. To categorize a patient as a complete responder after transplantation, residual masses had to remain unchanged for 6 months or longer.

A partial response (PR) was defined as a decrease greater than 50% of the sum of the products of the two longest diameters of all measurable lesions for at least 4 weeks, and non-measurable lesions also had to decrease by at least 50%. For patients to be considered in this category no lesions could increase in size and no new lesion could appear. A state of progressive disease (PD) was defined as any increase greater than 25% in the sum of the diameters of any measurable lesions or the appearance of a new lesion. We defined transplant-related mortality as death within 100 days of HDC/ASCT not related to the disease, relapse or progression. Standard variables to calculate the age-adjusted International Prognostic Index[13] and other variables of known prognostic importance, such as the MD Anderson tumor score,[14] were evaluated at the time of diagnosis and transplantation.

Statistical methods

Overall survival (OS), freedom from progression (FFP) and disease-free survival (DFS) were measured from the date of transplantation, and were estimated according to the Kaplan-Meier method.[15] Comparisons between the variables of interest at the time of transplantation were performed by the log-rank test.[16] All *p*-values reported were two-sided and statistical significance was defined at a *p*-value <0.05.

Results

Outcome

Response to transplant was as follows: 66% achieved a CR, 11% a PR, and in 20% of the cases the treatment failed. The disease response was not evaluated for 1 patient because of early death post-transplantation. After a median follow-up of the survivors of 37.5 months (range: 3-109), 18 patients out of the 35 transplanted (51%) were alive and 15 (43%) showed no evidence of the disease. Of the 17 patients who died, 12 (71%) died from progressive disease, 4 (24%) as a result of treatment-related causes, and 1 patient died from a second neoplasia while deemed to be free of lymphoma at this point. The transplant-related mortality was 11% (2 cases of adult respiratory distress syndrome, one sepsis, and one hepatic veno-oclusive disease). The actuarial OS at 5 years was 37% (95% confidence interval (CI), 16% to 58%), the FFP was 36% (95% CI, 17% to 55%), and the DFS for complete responders was 55% (95% CI, 30% to 80%: Figure 1).

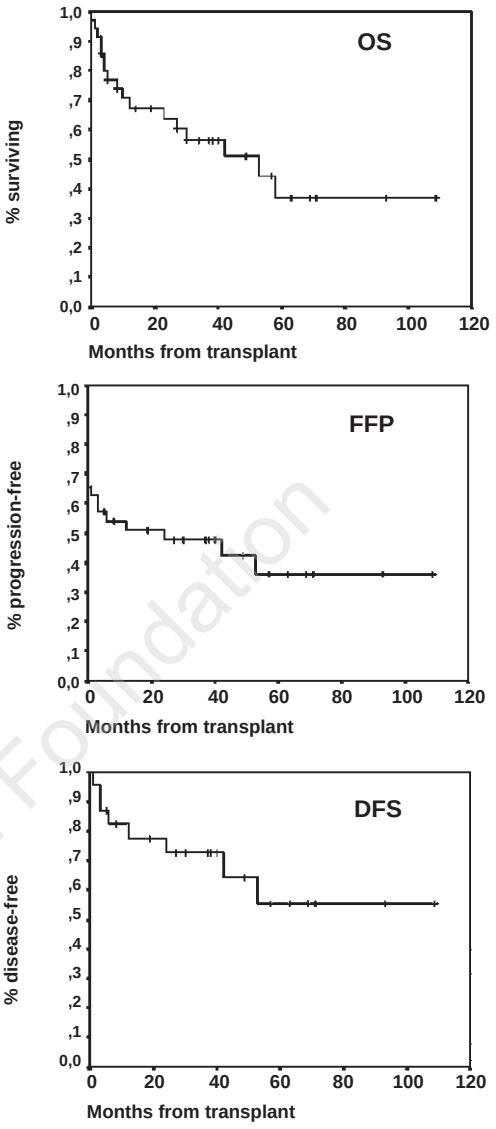

Figure 1. Overall survival, freedom from progression and disease-free survival.

Prognostic factors

Given the relatively small number of patients, we only performed univariate analysis to investigate which variables might be associated with the possible outcomes, including OS and FFP. We found that 2 or 3 aa-IPI risk factors, a tumor score >2,[14] and an elevated LDH at the time of transplantation were associated with reduced survival (Figure 2). However, we could not identify any factor at transplantation that provided prognostic information with respect to FFP.

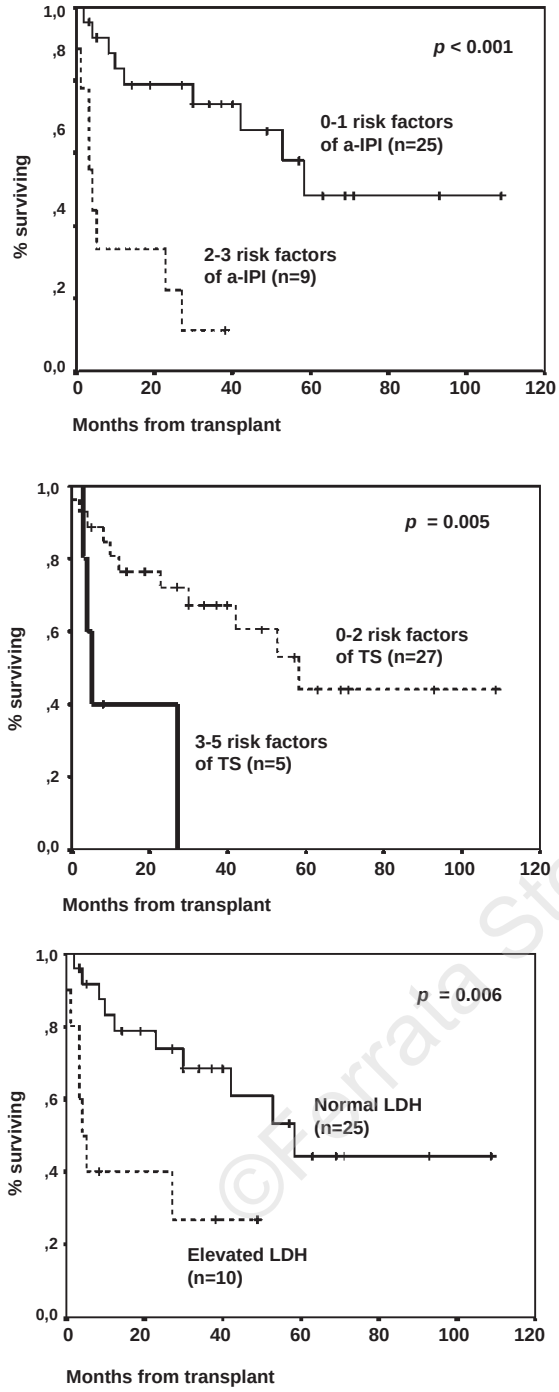

Figure 2. Overall survival according to age-adjusted International Prognostic Index, tumor score and lactate dehydrogenase level.

Discussion

The most recent series[5,17] of patients with advanced stages of aggressive NHL treated with standard protocols indicate that the T-cell immunophenotype confers an unfavorable prognosis, although similar outcomes were reported in older smaller series.[7] Patients with aggressive B-cell lymphomas who fail to respond to a first induction regimen have an approximately 30% possibility of being functionally cured with HDC/ASCT.[11,18] Nevertheless, whether this procedure is equally effective in patients with PTCL is much less clear. Recently, the Memorial group reported that they obtained similar outcomes with HDC/ASCT treatment in chemosensitive relapsed and primary refractory patients with PTCL and diffuse large B-cell lymphoma.[9] Indeed, the 4-year survival of both B- and T-cell groups were 46% and 34%, respectively (p=0.418) and the FFP was 33% and 22%, respectively (p=0.473). However only 7 patients in the PTCL group were primary refractory to the initial therapy, raising doubts about the validity of this effect.

Our data are from 35 patients with PTCL who failed to respond to standard induction chemotherapy for aggressive lymphomas, and who were registered in the GEL-TAMO database. Although most of the patients were chemosensitive (31 patients had had a first PR and only 4 were truly chemoresistant), the fact that 66% of these patients achieved a CR following transplantation is a similar outcome to that in our cohort of 74 patients with aggressive diffuse large B-cell lymphoma who failed to respond to induction therapy and who underwent HDC/ASCT.[19] Interestingly we did not observe significant differences in the OS, FFP and DFS between the 22 patients who only achieved a first PR but then obtained a CR following transplantation and the 37 patients who initially achieved a CR (*unpublished data*), suggesting that when patients are chemosensitive, HDC/ASCT may neutralize the adverse prognosis conferred by the failure of first line induction therapy. These data must be interpreted with caution since they are derived from a retrospective study and randomized prospective studies should be performed to evaluate this point fully. Unfortunately, all the patients with truly chemoresistant disease state failed to respond to the transplant, emphasizing the need to test other transplantation procedures or new therapeutic strategies for this fortunately small group of primary chemoresistant patients.

Our analysis showed that the aa-IPI and LDH at the time of transplantation could serve as prognostic factors for patients with this type of lymphoma. In our hands the tumor score[14] was a very useful means of separating patients with different outcomes. Moreover, Lee *et al*.[20] recently showed

that the tumor score had a better discriminatory value than that of the IPI in patients with early-stage PTCL treated with doxorubicin-based chemotherapy, with or without radiotherapy. This suggests that this risk system can be applied to this group of lymphomas as it takes into consideration the variables most related to the tumor rather than the host. The tumor score includes β2-microglobulin level as one of its variables, which is an important prognostic variable across the whole group of aggressive lymphomas, but which was not incorporated into the final analysis of the IPI project because of the absence of data for a large number of patients. Interestingly, more patients with PTCL presented high levels of β2-microglobulin than did those with corresponding aggressive B-cell lymphomas. No patient with more than two of the tumor score factors survived in our group of patients, another indication of the value of this risk system.

In spite of the retrospective design of this study and the limitations of a co-operative group registry, we conclude that chemosensitive patients with PTCL who fail to respond fully to induction seem to benefit from HDC/ASCT. Within this group of patients, those deemed to respond completely following the transplant have an excellent prognosis. The aa-IPI, LDH and tumor score at the time of transplantation were good means of predicting the outcome in this population of patients. Nevertheless, it seems that patients who failed to achieve at least a PR with front-line therapy did not benefit from HDC/ASCT. New therapeutic options should be tested in this small subset of patients. Finally, the results obtained from this group of patients with PTCL who failed to respond to induction do not differ from those observed in larger groups of patients with aggressive diffuse large B-cell lymphoma unresponsive to induction therapy.

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Pre-publication report

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JR was the principal investigator, responsible for the conception and design of the paper as well as the drafting and final approval of the paper; AG and MG contributed to the analysis and interpretation of data as well as the drafting of the manuscript; MDC, JS, AL, AS, JZ, JM, RA, EC, AL, AF and JS were responsible for the clinical management of the patients and their clinical data as well as for drafting the manuscript; EC critically revised the manuscript and gave final approval for its submission. The order of authorship reflects the contribution given to the study.

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Disclosures

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