Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma

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Aim: To analyze toxicity, response and outcome of a phase II trial with intensive chemotherapy plus autologous stem-cell transplantation (ASCT) for young patients with peripheral T-cell lymphoma (PTCL).

Patients and methods: Forty-one patients [30 males and 11 females, median age 47 years] consecutively diagnosed with PTCL received three courses of high-dose cyclophosphamide 2000 mg/m2/day, adriamycin 90 mg/m2/day, vincristine and prednisone alternating with three courses of etoposide, cisplatin, cytarabine and prednisone. Responders were submitted to ASCT.

Results: Sixty-eight percent of patients received the planned treatment. After chemotherapy, 20 patients reached complete response (CR), 4 partial response and 17 failed. ASCT was carried out in 17 of 24 candidates due to lack of mobilization (three cases), toxicity (two), early relapse and patient decision (one each). CR rate after treatment was 51%. With a median follow-up of 3.2 years, 5 of 21 CR patients relapsed and 2 died in CR due to secondary neoplasms. Four-year progression-free survival was 30%. Twenty-two patients have died, with a 4-year overall survival of 39%. International Prognostic Index was the main variable predicting survival. No differences were seen among the 24 candidates according to whether or not they underwent ASCT.

Conclusion: This intensive regimen resulted in moderate CR rate, with manageable toxicity in PTCL. The contribution of ASCT in preventing relapse is debatable. Novel strategies to increase CR warrant investigation.

Key words: autologous stem-cell transplantation, peripheral T-cell lymphoma, prognosis

introduction

Peripheral T-cell lymphoma (PTCL) and natural killer (NK)-cell lymphoma comprise a heterogeneous group of lymphoid neoplasms that constitute ~10% of lymphoid malignancies in Western countries [1, 2]. This proportion is higher in other countries due to epidemiological and genetic reasons [3]. Conversely to B-cell lymphomas whose classification on the basis of morphologic, immunophenotypic and genetic features is well established, the World Health Organization (WHO) classification of PTCLs warrants further refinements [1]. Thus, whereas subtypes such as anaplastic large-cell lymphoma (ALCL) [4] and angioimmunoblastic lymphoma [5] are well-defined entities, the most prevalent PTCL (30%–60% of them), the so-called ‘unspecified’ PTCL, contains a heterogeneous group of T-cell lymphomas not otherwise characterized. There is not a specific pattern of immunophenotyping or genetic features and the knowledge of the etiopathogenesis and the physiological counterpart of tumor cells is very limited.

From the clinical standpoint, with the exception of cutaneous PTCL and anaplastic large-cell-lymphoma kinase (ALK)-positive ALCL, most PTCLs share an aggressive behavior [6–11]. The majority of studies agree in that the outcome of PTCLs is worse than that of aggressive B-cell lymphomas [12–14]. For decades, the standard treatment of aggressive PTCL has been chemotherapy, with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) being the most popular regimen [10, 11]. The results of current therapies are, however, particularly poor in PTCL,
with a low complete response (CR) rate (10%–60%) and a median overall survival (OS) <3 years [6–14]. As for other aggressive lymphomas, different approaches to improve such figures have been attempted during the last years, including new drugs [15–17] and the increase of either the intensity or the density of chemotherapy. Better supportive measures, including granulocyte colony-stimulating factor (G-CSF), have allowed the use of more intensive treatments. In addition, the consolidation of the initial response by means of autologous stem-cell transplantation (ASCT) has been indicated to improve and maintain the response [18–25]. In this setting, the Grup per l’Estudi dels Limfomes de Catalunya i Balears (GELCAB) started a trial for young patients with aggressive PTCL that included intensive chemotherapy [high-dose CHOP alternating with conventional etoposide, cisplatin, cytarabine and prednisone (ESHAP)] followed, if any response, by ASCT. Thus, the rationale for the trial was (i) the use of intensified chemotherapy with the most active drugs in PTCL, in order to reach the highest CR rate, and (ii) to consolidate the eventual response with ASCT, in order to prevent relapse. Therefore, the aim of the study was to analyze the response to therapy and the outcome, as well as the toxicity, in a series of young patients with PTCL treated with this intensive approach.

patients and methods

patients

Forty-one patients diagnosed with a PTCL in six institutions of the GELCAB were included in the present study from January 1998 to January 2005. The eligibility criteria were the following: (i) histological diagnosis of PTCL, excluding mycosis fungoides and ALK-positive ALCL, (ii) age ≤65 years, (iii) Ann Arbor stage II, III or IV and (iv) absence of severe heart, liver or kidney disease, unless secondary to lymphoma. All the patients gave informed consent before the inclusion in the protocol. The study was approved following the institutional guidelines of the Ethical Committees. Median age of the patients was 47 years (range 20–65) and the male/ female distribution 30/11. Main initial characteristics of the patients at diagnosis are listed in Table 1.

treatment plan: chemotherapy, stem-cell harvesting and ASCT

The chemotherapy phase consisted of three courses of high-dose CHOP (cyclophosphamide 2000 mg/m²/day, day 1; adriamycin 90 mg/m²/day, day 1; vincristine 2 mg/day, day 1; prednisone 60 mg/m²/day, days 1–5; mesna (150% of the dose of cyclophosphamide) and (G-CSF) were used in all cases), alternating with three courses of standard ESHAP (etoposide 40 mg/m²/day, days 1–4; cisplatin 25 mg/m²/day, days 1–4; cytarabine 2000 mg/m²/day, day 5 and prednisone 250 mg/day, days 1–4).

All patients who reached a partial response (PR) or CR after chemotherapy were considered candidates for ASCT. The stem-cell harvesting was carried out after the second or third course of ESHAP. The stem-cell source was peripheral blood, after chemotherapy (ESHAP) and G-CSF. ASCT was carried out during the 3-month period after the end of chemotherapy. A minimum of 2.0 × 10⁹ CD34+ cells/kg was considered appropriate to safely carry out ASCT. Either carmustine, etoposide, cytarabine and cyclophosphamide (BEAC) or carmustine, etoposide, cytarabine and melphalan (BEAM) were acceptable regimens for conditioning.

staging maneuvers and assessment of response

Staging maneuvers consisted of physical examination (including Waldeyer’s ring area), blood cell counts and serum biochemistry, including lactate dehydrogenase (LDH) and β2-microglobulin levels, computerized tomography scan of chest, abdomen and pelvis and bone marrow biopsy. Post-therapy restaging consisted of the repetition of the previously abnormal tests and/or biopsies. A formal restaging was carried out after chemotherapy and after the whole procedure. Response was assessed according to conventional criteria [26].

histological revision

In addition to the diagnosis made in each institution, the histological slides have been centralized reviewed by three different observers (LC, IE and SM), in order to confirm the diagnosis according to the WHO classification. Morphologic subclassification was carried out as previously described [1].

statistical considerations

The main end point of the study was overall CR rate. Secondary end points were progression-free survival (PFS), event-free survival (EFS), OS and toxicity. The sample size was calculated according to the optimal two-stage design for phase II clinical trials according to the following assumptions: \( P_0 = 40\%\) CR and \( P_1 = 60\%\) CR, with alpha and beta errors of 0.05 and 0.10, respectively [27]. PFS, EFS and OS were defined according to standard criteria [26]. Categorical data were compared using the Fisher’s exact test, two-sided \( P \) value, whereas nonparametric tests were used for ordinal data. Bonferroni correction for multiple comparisons was applied when necessary. Multivariate analysis of the variables predicting response was carried out by using a logistic regression. The actuarial survival analysis was carried out according to the method described by Kaplan and Meier [28] and the curves compared by the log-rank test [29]. The multivariate analysis

<table>
<thead>
<tr>
<th>Table 1. Main features of 41 patients with peripheral T-cell lymphoma (PTCL) at diagnosis</th>
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<tr>
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<tr>
<td>Age ≤50 years</td>
</tr>
<tr>
<td>Primary extranodal</td>
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<tr>
<td>Poor performance status</td>
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<tr>
<td>(ECOG &gt;1)</td>
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<tr>
<td>B symptoms</td>
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<tr>
<td>Extraneal involvement</td>
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<tr>
<td>0 sites</td>
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<tr>
<td>1 site</td>
</tr>
<tr>
<td>&gt;1 site</td>
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<tr>
<td>Bone marrow involvement</td>
</tr>
<tr>
<td>Ann Arbor stage IV</td>
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<tr>
<td>High-serum LDHa</td>
</tr>
<tr>
<td>High-serum β2-microglobulin*</td>
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<tr>
<td>International Prognostic Index</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Low/intermediate risk</td>
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<tr>
<td>High/intermediate risk</td>
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<tr>
<td>High risk</td>
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<td>Italian Index for PTCL</td>
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<td>Group 1</td>
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<td>Group 2</td>
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<td>Group 3</td>
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<td>Group 4</td>
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</tbody>
</table>

*LDH and β2-microglobulin were available in 40 and 39 cases, respectively. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.
analysis for survival was carried out by using the stepwise proportional hazards model (Cox) [30].

**results**

**initial features of the patients**

The main characteristics of the 41 patients (30 males and 11 females, median age 47 years) at the time of inclusion are detailed in Table 1. The histological distribution was as follows: PTCL unspecified, 20 cases (49%); angioimmunoblastic, 12 cases (29%); γδ hepatosplenic, 2 cases (5%); other γδ PTCL, 1 case (2%); extranodal NK nasal type, 2 cases (5%); s.c. panniculitis like, 2 cases (5%) and Sézary syndrome and ALK-positive ALC, 1 case each. The latter was included in the trial on the basis of the poor-risk characteristics of the patient.

The disease was primarily extranodal in 12 cases (29%), including skin (5 cases), Waldeyer’s area (2 cases), bone marrow, lung, bone plus marrow and liver plus pleura (1 case each). Bulky mass was seen in two patients. Ann Arbor distribution was the following: stage I, 5 cases (12%); stage III, 7 (17%) and stage IV, 29 (71%). Fourteen patients had bone marrow involvement and four leukemic expression of the disease. The distribution according to International Prognostic Index (IPI) for aggressive lymphomas [31] and the Italian Index for PTCL (groups 1–2 versus 3–4) were included in Table 1.

**chemotherapy phase (high-dose CHOP/ESHAP)**

A total of 217 courses of chemotherapy (high-dose CHOP, 113; ESHAP, 104) were administered. Twenty-eight patients (68%) received the planned six courses of therapy, six (15%) received five and seven (17%) received less than five courses.

Hematological toxicity mainly consisted of neutropenia (grades 3–4 in 63% and 68% after high-dose CHOP and ESHAP, respectively) and thrombocytopenia (grades 3–4 in 20% and 26%, respectively). Median nadirs after chemotherapy are listed in Table 2. Severe infection requiring hospitalization was observed in 38% and 15% of courses of high-dose CHOP and ESHAP, respectively. Main infection episodes included sepsis (15 episodes, including eight by *Enterobacteriaceae*, four by *Staphylococcus Aureus* and three by other germs), pneumonia (2 cases), *Pneumocystis Jiroveci* pneumonia and chronic systemic candidosis (1 case each). One patient died of sepsis during the aplasia after the first course of high-dose CHOP. No unexpected extrahematological toxic effects were observed.

<table>
<thead>
<tr>
<th>Median nadir (range)</th>
<th>Mega-CHOP (n = 113)</th>
<th>ESHAP (n = 104)</th>
<th>ASCT (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count (x10⁹/l)</td>
<td>0.01 (0–1.2)</td>
<td>0.4 (0–2.2)</td>
<td>0.01 (0–0.2)</td>
</tr>
<tr>
<td>Platelet count (x10⁹/l)</td>
<td>23 (1–129)</td>
<td>29 (3–158)</td>
<td>5 (0–11)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>7.8 (5.1–12)</td>
<td>8.6 (6.2–12)</td>
<td>8.7 (7.0–10.0)</td>
</tr>
</tbody>
</table>

CHOP, cyclophosphamide, adriamycin, vincristine and prednisone; ESHAP, etoposide, cisplatin, cytarabine and prednisone.

After chemotherapy, 16 patients achieved CR (39%), 4 CR/unconfirmed (CR[u]) (10%) and 4 PR (10%), whereas therapy failed in 17 (in 16 cases because of disease progression and in 1 due to an early death by sepsis as previously mentioned).

In one patient diagnosed with extranodal NK nasal type, radiotherapy was administered after chemotherapy and before ASCT.

The outcome of the 16 patients who showed primary refractoriness to mega-CHOP/ESHAP was extremely poor, with a median OS of 8 months. Salvage therapy was administered in 12 of these patients, including the regimen high-dose ifosfamide, etoposide and prednisone in most cases and intensification with ASCT (one case) or allogeneic stem-cell transplantation (two cases). Only one patient (8%) reached a CR (after rescue and ASCT) that lasted for 5.0 years.

**autologous stem-cell transplantation**

Twenty-four patients (16 CR, 4 CR[u] and 4 PRs) were candidates for ASCT after the chemotherapy phase. However, in seven patients different reasons precluded transplantation: in three cases due to a failure in harvesting, in two because of poor performance status due to previous toxicity, in one due to early relapse of the lymphoma and in the last case because of the patient decision. Thus, intensification was finally carried out in 17 patients. In addition, one of these patients had an identical twin donor and, for this reason, singenic transplantation was carried out in this particular case.

Harvesting was successful in 16 of 19 cases, with a median number of CD34-positive cells of 3.5 x 10⁹/kg (range 1.98–20). The median number of mobilization procedures was one (range 1–3). Peripheral blood was the source of hematopoietic progenitors in all cases. BEAC was the conditioning regimen in 5 patients and BEAM in 12. No major toxic effects were observed during the ASCT procedures. The nadirs of hemoglobin, neutrophil and platelet counts are detailed in Table 2. Eight of 16 patients (50%) presented with grade 3/4 infections. Time to neutrophil recovery >0.5 x 10⁹/l and >1.0 x 10⁹/l were 11 days (range 9–36) and 12 days (range 9–50), respectively. Time to platelet recovery >20 x 10⁹/l and >50 x 10⁹/l were 14 days (range 7–36) and 19 days (range 9–50), respectively.

After ASCT, patients in CR and CR[u] maintained the response status, whereas one patient in PR reached CR.

**response to therapy**

Overall, the best response after the whole procedure was CR 17 patients (41%), CR[u] 4 patients (10%) and PR 3 patients (7%). The only initial variable predicting CR achievement was performance status [CR rate for patients with Eastern Cooperative Oncology Group (ECOG) <2 and ≥2 were 73% and 26%, respectively; P = 0.005]. In addition, IPI and Italian Index for PTCL also were able to predict CR achievement.

When IPI (low versus intermediate versus high risk) and Italian Index for PTCL (groups 1–2 versus 3–4) were included in a logistic regression, only IPI maintained significance [relative risk (RR) 5.4; P = 0.01]. The number of courses of chemotherapy administered to the patients also showed...
predictive value for CR, with those patients receiving less than six courses having a lower CR rate than those receiving the planned therapy (CR rate: 8% versus 71%, respectively; \( P = 0.0002 \)).

**survival**

After a median follow-up for surviving patients of 3.2 years (range 0.6–8.1), 5 of 21 CR patients eventually relapsed. In addition, two patients died in CR due to secondary neoplasms (Burkitt-type acute lymphoblastic leukemia and metastatic lung adenocarcinoma at 0.7 and 2 years from CR achievement, respectively). Thus, the 4-year EFS for CR patients was 59% [95% confidence interval (CI) 35–83] (Figure 1). Overall, 27 of 41 patients eventually progressed, with a 4-year PFS of 30% (95% CI 15–45) (Figure 2).

Twenty-two patients died during follow-up. The causes of death were progression of the disease in 19 cases, death in CR due to malignancies other than PTCL in 2 cases and sepsis during induction therapy in 1 case. In Figure 2, OS curve of the present series is plotted. Four-year OS was of 39% (95% CI 22–56). Variables predicting poor OS were the following: presence of B symptoms \(( P = 0.016 \)) , poor performance status (ECOG >1) \(( P = 0.0001 \)) , leukemic expression \(( P = 0.05 \)) , low serum albumin \(( P = 0.01 \)) and high serum LDH \(( P = 0.02 \)) . Angioimmunoblastic histology showed a trend for a poor outcome (4-year OS for angioimmunoblastic versus other PTCL: 18% versus 48%, respectively; \( P = 0.09 \)). IPI also showed to be important to predict OS \(( P = 0.005 \)) , whereas the Italian Index for PTCL and age >50 years only showed a trend \(( P = 0.07 \) in both cases). A multivariate analysis was carried out with initial variables, including IPI (low versus intermediate versus high risk), serum albumin and B symptoms. In the final model that included 39 cases, only IPI retained prognostic significance \(( P = 0.001 \); RR 3.5). Moreover, when IPI and Italian Index for PTCL were put together in a Cox analysis, only IPI maintained the prognostic value for OS.

Among evolutive variables, CR achievement after chemotherapy resulted, as expected, the most important evolutive variable to predict OS. Interestingly, no differences were found in terms of OS whether ASCT was carried out or not in the 24 patients in CR or PR candidates for this procedure (Figure 3).

The main features of nine patients surviving for >4 years are listed in Table 3. Of note, eight of nine patients reached CR after chemotherapy, and all but one patient eventually received ASCT. No other particular characteristic was present in this particular subset of patients.

**discussion**

In this study, we have shown that a moderate CR rate could be obtained with intensive chemotherapy followed by ASCT in selected young patients with aggressive PTCL. Although it would be desirable to conduct clinical trials for specific varieties of T-cell lymphomas, as in B-cell lymphomas, this is difficult for a number of reasons, among them the fact that many of these tumors are infrequent and also the lack of reproducible criteria for its identification [1–10]. Thus, the histological distribution of the series is heterogeneous reflecting that the trial was designed for all the subtypes of aggressive PTCLs, only excluding cutaneous forms and ALK-positive ALCL. In this regard, it is interesting to note that histological subgroup did not convey any significant difference in terms of OS,
Table 3. Characteristics of nine peripheral T-cell lymphoma patients with survival >4 years

<table>
<thead>
<tr>
<th>Age (years)/sex</th>
<th>Histological subtype</th>
<th>Stage</th>
<th>Response to chemotherapy</th>
<th>Intensification therapy</th>
<th>OS (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42/F</td>
<td>Unspecified</td>
<td>IV</td>
<td>CR</td>
<td>ASCT</td>
<td>4.3+</td>
</tr>
<tr>
<td>53/M</td>
<td>Unspecified</td>
<td>IV</td>
<td>CR</td>
<td>ASCT</td>
<td>4.4+</td>
</tr>
<tr>
<td>54/F</td>
<td>Angioimmunoblastic</td>
<td>IV</td>
<td>CR</td>
<td>ASCT</td>
<td>4.4+</td>
</tr>
<tr>
<td>24/M</td>
<td>Unspecified</td>
<td>IV</td>
<td>CR</td>
<td>Singenic SCT</td>
<td>4.5+</td>
</tr>
<tr>
<td>53/M</td>
<td>Unspecified</td>
<td>II</td>
<td>No CR</td>
<td>ASCT (salvage)</td>
<td>5.1+</td>
</tr>
<tr>
<td>54/M</td>
<td>Panniculitis like (αβ)</td>
<td>IV</td>
<td>CR</td>
<td>ASCT</td>
<td>5.2+</td>
</tr>
<tr>
<td>65/M</td>
<td>Angioimmunoblastic</td>
<td>II</td>
<td>CR</td>
<td>No</td>
<td>5.6+</td>
</tr>
<tr>
<td>55/F</td>
<td>Angioimmunoblastic</td>
<td>II</td>
<td>CR</td>
<td>ASCT</td>
<td>6.0+</td>
</tr>
<tr>
<td>52/F</td>
<td>Panniculitis like (αβ)</td>
<td>IV</td>
<td>CR</td>
<td>ASCT</td>
<td>8.1+</td>
</tr>
</tbody>
</table>

OS, overall survival; F, Female; CR, complete response; ASCT, autologous stem-cell transplantation; M, Male; SCT, stem-cell transplantation.

although patients with angioimmunoblastic lymphoma showed a trend for a shorter survival. Preliminary data indicate that gene expression profiling and cytokines and cytokine receptors expression could be of help to separate these groups [33–36].

In contrast with the important advances in the treatment of B-cell lymphomas, management of patients with PTCL is disappointing, with no major progress over the last decades. Some reasons to explain this fact are the relatively rarity of PTCLs, the absence of common markers to use mAb therapy, the lack of randomized trials, the geographical variations and, certainly, the genuine drug resistance of these lymphomas. PTCLs treatment is still on the basis of the same premises than that of B-cell aggressive lymphomas, largely on the basis of the CHOP or CHOP-like regimens. These treatments result in a variable CR rate generally inferior to 50%, with a 5-year OS of <30% in the majority of the series, with the exception of patients with ALK-positive ALCL. To improve these results, it would be necessary both to increase CR rate and to reduce the risk of relapse. Dose-intense and dose-dense chemotherapies such as the French adriamycin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) [13] and the hyper-fractionated cyclophosphamide, vincristine, adriamycin and dexamethasone [37] regimens have been investigated in several trials, the results being not satisfactory. In a Groupe d’Etude des Lymphomes Agressifs randomized trial that included B-cell and T-cell aggressive lymphomas, ACVBP showed advantage over CHOP in terms of OS in the subset of PTCLs [38]. However, since that study was not designed for PTCL patients, its results are not completely reliable.

In our study, intensive chemotherapy (high-dose CHOP plus ESHAP) was feasible with a high but manageable toxicity. The CR rate (50%) was, however, lower than expected in young patients. As a matter of fact, the CR rate was not much higher than that previously reported in a historic Spanish series of patients treated with CHOP-like regimens [8]. Furthermore, in a retrospective analysis by the International PTCL Clinical and Pathologic Review Project, an apparent lack of efficacy of anthracyclines has been pointed out, at least in terms of OS [39]. These data indicate that more intense/dense regimens do not necessarily overcome the poor prognosis of PTCL patients. ASCT might have a role as part of the front-line therapy in PTCL increasing CR and reducing relapses. In retrospective studies, those patients in whom an ASCT was carried out had a favorable outcome, with OS >65% at 5 years [18–20,22–24]. In some prospective phase II series, results have also been encouraging. In all these studies, however, a significant proportion of patients could not eventually be transplanted due to the poor response to chemotherapy, with this being an important selection bias in studies aimed at evaluating the role of ASCT. In our series, 58% of the patients were candidate to ASCT and only 41% were eventually transplanted. OS of transplanted patients (58% at 5 years; Figure 3) was similar to other series [18–20], whereas median OS of the remainder patients did not reach 1 year. Regarding allogeneic stem-cell transplantation, the experience is limited to small series of highly selected patients. Fully myeloablative allogeneic transplantation conveys an important toxicity and transplant-related mortality. Because of this, there is an increasing interest in reduce-intensity conditioning allogeneic transplantation, but its exact role in PTCL has to be determined in the following years [40, 41].

In PTCL patients, a number of prognostic factors have been identified [6–11]. IPI has been successfully applied and the Italian score [31], specifically developed for these patients, is also useful. In the series reported in this article, IPI had predictive value whereas the Italian score, although to a lower degree, was also significant. More recently, a new score has been built up by incorporating the proliferation index as assessed by Ki-67 expression [42].

In conclusion, in this series of patients with PTCL a moderate CR rate was obtained with high-dose CHOP/ESHAP followed by ASCT. Toxicity was manageable. The contribution of ASCT to the outcome of the patients is debatable because of the absence of significant differences in OS and EFS of patients in CR transplanted versus those not transplanted. Novel strategies aimed at increasing the CR rate in these patients warrant investigation.

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references


