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Autologous stem cell transplantation in advanced follicular lymphoma. A single center experience

ROSARIO LÓPEZ, RODRIGO MARTINO, ANNA SUREDA, JOSEP NOMDEDÉU, JAVIER BRIONES, GREGORIO MARTIN-HENAO,* JUAN GARCÍA,* SALUT BRUNET, JORGE SIERRA
*Clinical Hematology Division, Hospital de la Santa Creu i Sant Pau; *Institut de Recerca Oncològica, Barcelona, Spain*

ABSTRACT

Background and Objective. **The use of intensive therapy supported by autologous stem cell transplantation (ASCT) is being investigated as treatment for poor-prognosis follicular lymphomas (FL). A single-center experience is herein reported.**

Design and Methods. **From September 1990 to October 1997, 30 consecutive patients (pts) with advanced FL received transplants, 8 of bone marrow and 22 of peripheral blood. Thirteen harvests were purged by an immunomagnetic method using anti-B antibodies. Twenty-seven patients received salvage chemotherapy (CT) before ASCT with the objective of reaching this procedure in the best possible response. The disease status at ASCT was: 1st CR in 7 pts, ≥2nd CR in 6 pts, PR in 10 pts, untreated relapse in 2 pts and chemoresistant disease in 5 pts.**

Results**. There was only one transplant-related death (one month after ASTC). With a median follow-up of 19 (1-89) months, 27 pts are alive, 8 pts have relapsed / progressed at a median time of 11 (6-22) months after ASCT. The estimated 2-year PFS and OS are 57% (95% CI, 34-81%) and 83% (95% CI, 64-100%). When comparing the progression-free interval (PFI) before salvage CT and ASCT and the PFI after ASCT, of 17 evaluable pts, 10 had a PFI after ASCT longer than the previous interval, and 5 additional pts remain in CR / PR with a follow-up that has not yet reached the duration of pre-transplant response. By contrast, 2 pts had a short post-transplant response.**

Interpretation and Conclusions. **High-dose therapy followed by ASCT obtains a high rate of responses, frequently longer than any previous PFI. Additional follow-up is necessary to determine whether there is any "plateau" in response duration and to define what proportion of pts may be cured with ASCT in this setting.**

Key words: ASCT, follicular lymphoma

Correspondence: Rosario López, M.D., Servei d'Hematologia Clínica, Hospital de la Santa Creu i Sant Pau, Av. Sant Antoni Maria Claret, 167, 08025 Barcelona, Spain.
Phone: international + 34-3-2919396 – Fax: international + 34-3-2919466 – E-mail: 28429rls@comb.es

Follicular lymphomas (FL) are the most frequent of the low-grade or indolent lymphomas. Even in advanced stages, FL usually respond to initial conventional chemo-radiotherapy, but subsequent relapse or progression occurs in virtually all patients over the following months. Durable remissions are infrequent and progression to an advanced, unresponsive phase is almost constant.[1-3] The use of intensive therapy supported by autologous hematopoietic stem cell transplantation (ASCT) is being investigated in FL. Young patients with advanced disease and expected short progression-free and overall survival seem to be the best population for this procedure, with the hope of prolonging these intervals. Although initial results of ASCT appeared promising, the indolent course of these lymphomas precludes any definite conclusions based on short-term observations.[4-14] For this reason the benefit of ASCT in FL remains unproven. Greater complexity has been added with the introduction of sophisticated *in vitro* purging methods aimed at eliminating lymphoma cells. The clinical impact of using these purged products is controversial.[14-16]

We studied the role of high-dose therapy supported by ASCT in patients with primary refractory or relapsed advanced FL. The main parameter analyzed was whether the progression-free interval (PFI) after transplantation was longer than the last PFI before the procedure. We also evaluated overall survival (OS), progression-free survival (PFS) and procedure-related toxicity.

Design and Methods

Inclusion criteria

Patients with advanced FL defined according to the REAL classification were eligible for ASCT, with central histology review for referred patients; histologic samples from patients treated before 1995 were reviewed to confirm the diagnosis of FL according to the REAL classification. Patients with relapsed or refractory disease, and patient in first response if refractory to front-line CT with CHOP, were included. Only exceptionally were patients with FL transplanted for chemoresistant disease. Most consecutive patients treated at our institution with relapsed

Table 1. Patients' characteristics.

Characteristics	*No.*
Total no. of patients	30
Sex	17 M /13 F
Median age (range)	45 yrs. (30-62)
Histology	
Follicular, nodular	24
Follicular, diffuse	4
Follicular, transformed to DLCL	2
Stage at diagnosis	
II	1
III	7
IV	22
Median time from diagnosis to ASCT (range)	29 mo.(11-97)
Median number of prior CT regimens (range)	2 (1-4)
Prior radiotherapy	3
Salvage therapy pre-ASCT	27
Disease status at ASCT	
1st complete remission	7
≥2nd complete remission	6
1st partial remission	4
2nd partial remission	6
Untreated relapse	2
Chemoresistant	5
BMT	8
Purged	4
Unpurged	4
PBSCT	22
Purged	9
Unpurged	13

DLCL: diffuse large cell lymphoma; ASCT: autologous stem cell transplant; CT: chemotherapy.

FL were eligible, provided that they had chemosensitive or untreated disease, and that at least 2×10^8/kg nucleated cells were available for BMT or 2×10^6/kg $CD34^+$ cells for peripheral blood stem cell transplantation (PBSCT). No transplantation for FL at our institution has been excluded from this report.

Patients

Patients had to be between 18 and 65 years of age and have adequate organ function in order to undergo ASCT. Thirty patients were judged appropriate candidates and received an ASCT between September 1990 and October 1997. The main characteristics of the series appear in Table 1. Twenty-seven patients received salvage CT before ASCT with the objective of reaching the transplant in the best possible response; most of these patients (n=23) received the IAPVP-16 regimen.[17] Restaging confirmed the achievement of at least a PR in 23 cases and less than a PR in four cases.

Bone marrow and peripheral blood stem cell harvests

BM harvest was done in eight patients, while the remaining 22 received PBSC. Thirteen harvests (4 BM and 9 PBSC) were immunologically purged using immunomagnetic beads coated with sheep anti-mouse immunoglobulins (Dynabeads® M450, Dynal, Oslo, Norway) and a cocktail of monoclonal antibodies CD19, CD20, CD22, CD23 and CD37 (Baxter®).[18,19] Results of the purging strategy were analyzed with nested PCR amplification of the major breakpoint region (MBR) and minor cluster region (mcr) of the bcl-2/IgH rearrangement for t(14;18) translocation, both in initial, adsorbed (positive) and final fractions. The log depletion was calculated as the log of the ratio of initial absolute number of target antigen-positive cells/final absolute number of target antigen-positive cells.

The median number of nucleated cells (NC) and $CD34^+$ cells infused are given in Table 2. The B-cell depletion obtained with the immunomagnetic method ranged from 1.37 to >2.02 log reduction (median >1.86) in ABMT and 0.3 to >2.13 log (median >1.23) in PBSCT, with a median yield of 64.5% (range 53.2-74) NC and 78.5% (range 63.8-94.1) $CD34^+$ cells during the purging procedure in the case of ABMT. In APBSCT the median NC yield was 76.9% (range 64.7-87.5) and the median $CD34^+$ cells yield 71.6% (range 61.5-98.6).

Conditioning regimen

Twenty-nine of the 30 patients received cyclophosphamide (60 mg/kg on two consecutive days) plus hyperfractionated TBI (2-2.5 Gy per fraction, twice daily on three consecutive days for a total of 12-13.5 Gy). One patient received the BEAM regimen (BCNU, VP-16, Ara-C and melphalan). After ASCT one

Table 2. Results of bone marrow and peripheral blood stem cell harvests.

	Bone marrow				Peripheral blood stem cells			
	Total	*Unpurged*	*Purged*	*p*	*Total*	*Unpurged*	*Purged*	*p*
Nucleated cells/kg (10^8)								
Median	1.50	2.77	0.47	0.2	5.79	8.01	3.53	0.03
Range	0.14-17.80	1.90-17.80	0.14-1.10		1.83-12.80	2.25-12.80	1.83-7.41	
$CD34^+$/kg (10^6)								
Median	1.60	5.23	1.39	0.4	7.71	12	6.50	0.05
Range	0.66-8.90	1.57-8.90	0.66-2.70		3.80-44.10	3.80-44.10	3.80-16.40	

patient received local radiotherapy due to pre-transplant bulky abdominal disease.

Supportive measures

Patients were treated in private rooms with reverse isolation and a diet low in bacteria and fungi. They did not receive either antibacterial or antifungal prophylaxis; antiviral prophylaxis consisted of oral acyclovir. Parenteral antibiotics were started if there was fever ≥ 38ºC during neutropenia and maintained until the patient was apyrexial for at least 3 days. Granulocyte colony-stimulating factor (G-CSF) was given when clinically indicated.

Response criteria

Before and 3 and 12 months after ASCT, disease response was assessed with standard radiologic and histologic methods and was defined as follows: complete remission (CR) was when there was no measurable disease and no BM involvement by conventional histology; partial response (PR) consisted of decrease by at least 50% of all measurable lesions before treatment with BM involvement of less than 20%; the no response (NR) category included cases not qualifying for PR or progressive disease (PD); finally, PD reflected involvement of new sites after treatment, recurrence in originally involved sites, increase by more than 25% in original tumor masses and/or reappearance of detectable BM involvement.

Statistical considerations

The main parameters analyzed were transplant-related toxicity, response, progression-free interval, comparison of PFI after ASCT with the last PFI pre-ASCT to assess possible conversion of remission duration by the transplant, PFS (interval from day of ASCT until relapse, disease progression, death or last follow-up) and OS (interval from the day of ASCT until death or last follow-up). The closing date for analysis was March 31, 1998. Continuous variables were compared by non-parametric tests (Mann-Whitney's U test). Time dependent events were analyzed with the Kaplan-Meier method, and the log-rank test was used to assess univariable prognostic factors. Multivariable analysis was performed by means of the Cox proportional hazards method.

Results

Hematologic recovery

All patients engrafted (ANC >0.5×10^9/L) at a median of 14 (range 9-31) days and recovered platelets >20×10^9/L at a median of 14 (7-70) days post-transplant. The median times to neutrophil and platelet recovery in purged and unpurged SCT were: neutrophils on day +14 (10-31) and +13 (9-17) (p= NS), respectively; platelets on day +17 (8-70) and +13 (7-46) (p= NS), respectively. APBSCT recipients and ABMT recipients engrafted neutrophils at a median of 13 (9-31) days and 15 (11-25) days post-trasplant (*p*=NS), respectively; platelet recovery occurred at a median of 13 (9-46) days and 24 (13-70) days (*p*=0.005), respectively.

Toxicity

After ASCT 29 of 30 (97%) patients developed neutropenic fever, with two cases of pneumonia. There was one transplant-related death (3%) due to idiopathic pneumonia, one month after ASCT. There were no other significant procedure-related toxicities, nor have there been any late complications such as secondary myeloid malignancies.

Response and survival after ASCT

One patient died (day +37) and was unevaluable for response. Disease status at various time intervals in the remaining 29 patients is shown in Table 3. At 3 months post-transplant 24 patients were in CR (including 13 patients who were in CR before transplant), four in PR and one was not evaluated at 3 months. Eight patients have progressed or relapsed at a median of 11 months after the procedure (range 6 to 22 months); two of them have died, one is in CR at 46 months+ after cranial irradiation of a central nervous system relapse and the other five are alive with disease at a median of 16 months (8-22) from progression. One of the patient with transformed disease is alive in remission and the other is dead from progression. With a median follow-up of 19 (1-89) months, 27 patients are alive, 20 in CR, two in PR and five with active disease under palliative therapy. Figures 1 and 2 show the Kaplan-Meier curves for PFS and OS after ASCT. The median OS after ASCT has not been reached, and the estimated 2-year PFS and OS are 57% (95% CI, 34-81%) and 83% (95% CI, 64-100%), respectively.

Univariable and multivariable analyses performed to identify prognostic factors for progression after transplantation included age (< and ≥ 45 years), sex, time from diagnosis to ASCT (< and ≥ 29 months), disease status at ASCT (CR vs. not in CR), number of

Table 3. Outcome following ASCT.

	Pre-ASCT nº (%)	*After ASCT 3 months nº (%)*	*Last follow-up* nº (%)*
Complete remission	13 (43)	24 (80)	20 (67)°
Partial remission	10 (33)	4 (13)	2 (7)°
Chemoresistant	5 (17)	–	–
Alive with progressive disease	–	–	5#
Untreated relapse	2 (7)	–	–
Treatment–related death	–	1	1
Progression–related death	–	–	2#
Patients not evaluated for response	–	1	–

**Median of 19 (1–89) months; °median follow–up for patients in CR/PR: 17 (1-89) months; #median time to progression: 11 (6-22) months (one patient is in CR after cranial irradiation). ASCT: autologous stem cell transplant.*

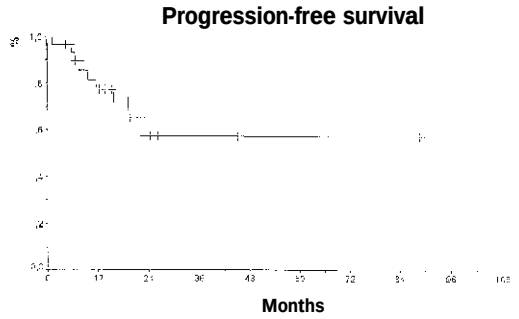

Figure 1. Progression-free survival.

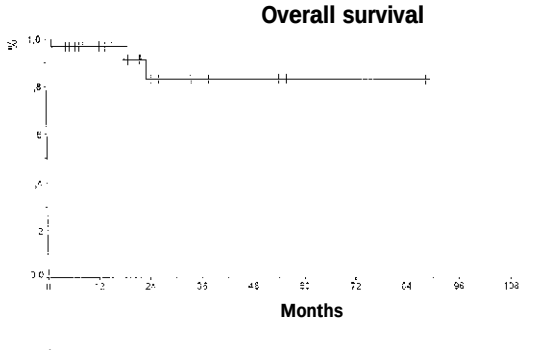

Figure 2. Overall survival.

have obtained response conversion and five are in CR but have not reached the conversion duration, while two patients had a shorter time PFI post-transplant than the pre-ASCT interval.

Discussion

Our results confirm the high rate of responses obtained with ASCT for patients with advanced FL. Thus, three months post-transplant, 86% of the patients were in CR and 14% in PR, with improvement in response (PR to CR, or NR to PR/CR) in 14 cases. With a median follow-up of 19 months, 67% remain in CR and 7% in PR. Additionally, among 17 patients evaluable for remission conversion, 10 have had a conversion of the PFI after the transplant, while five are too early but remain in remission. The main handicap of our study is the relatively short follow-up after transplant. In most previous studies, despite high rates of response after transplant, a continuous rate of relapse/progression is subsequently observed.[4-12] Furthermore, there is no evidence that OS is prolonged, and ASCT may simply prolong PFS in absence of an impact on survival. Unfortunately, without controlled studies any modification in OS cannot be proven.

Our patients have an estimated 2-year PFS and OS of 57% and 83%, respectively. Previous studies which included from 21 to 100 cases reported PFS of 53% to 75% at 2 years and 44% to 55% at 4 years, while the estimated OS rates ranged from 80% to 90% and 65% to 75%, respectively.[4-14] As stated, however, relapses continue to occur even more than 5 years after the procedure, and longer follow-up is needed to see whether a plateau in PFS occurs. One difficulty in comparing our results with those from other institutions is that the patient characteristics, stem cell sources, conditioning regimens and purging methods have varied markedly. For instance, while we attempted to include only patients with chemosensitive disease, others have autografted more chemoresistant cases, with shorter PFS and OS.[9,13] Even in chemosensitive patients, however, bad results have been reported; for instance, Verdonck *et al.* recently reported on 18 patients with chemosensitive FL who underwent an ASCT, and who had 2-year DFS and OS of 22% and 33%, respectively.[20]

Transplant-related mortality (TRM) was low in our experience, with there being only one such event, giving a rate similar to the currently accepted one of less than 5% in patients autografted for lymphoid malignancies.[10] Also important, we have not observed any late complications such as secondary myelodysplasia or AML, which have raised significant concern in other institutions.[8,21-23] However, the median time for developing these myeloid malignancies was 34 months (range 5-101) in those studies, and we may see such late complications in the future, especially when considering that most of our patients were heavily pretreated before ASCT.

It is of the utmost importance to identify which patients are most likely to benefit from an ASCT, at least in terms of prolonged PFS. In our patients, none of the variables analyzed were predictive of progression after the procedure. This may be due to the fact that only eight progressions have occurred post-transplant, and that the numbers of patients in each group are small. In previous studies few factors predicting outcome have been consistently identified, although in two independent series the number of previous CT regimens correlated with the risk of

Table 4. Comparison of last PFI and post-ASCT PFI.

Evaluable for conversion	
PFI post-ASCT longer than last PFI before ASCT	10 pts
CR/PR but have not reached the conversion duration of response	5 pts
PFI post-ASCT shorter than the last PFI before ASCT	2 pts
Not evaluable for conversion	
ASCT in first response	5 pts
Early TRM	1 pt
Primary refractory cases in CR/PR after ASCT	7 pts

PFI: Progression free interval. ASCT: Autologous stem cell transplant. TRM: Transplant related mortality.

relapse failure.[8,9] Investigators from the Dana-Farber Cancer Institute studied the influence of various clinical and biologic parameters on the duration of PFS and OS both in relapsed FL[15] and in high-risk patients in first remission.[5] In both situations, bcl-2 rearrangement negative BM studied by a sensitive PCR method and/or a persistent negativity of the patient's BM and peripheral blood by PCR post-transplant were associated with prolonged progression-free survival, while positive PCR post-transplant predicted relapse. The Turin Group reported their experience with molecular monitoring of minimal residual disease after ASCT in follicular and mantle cell lymphomas, and concluded that autografting with PCR-negative harvest is associated with durable clinical and molecular remissions.[24] Other investigators have not found this correlation between PCR-negativity of the infused stem cells or of the patients' BM or peripheral blood post-ASCT and the PFS,[8,14,16] suggesting that the inability to purge the stem cells or to obtain a PCR negative state after the procedure may be a surrogate marker for a more aggressive disease.[25] We did not look at this aspect in the current study and the role of bcl-2 status on the results of ASCT is now being prospectively evaluated at our institution.

In conclusion, in our experience ASCT for advanced FL obtains high rates of clinical responses and frequent remission inversions. Early TRM is low. Longer follow-up is necessary to identify any late complications, as well as to determine the rate of long-term PFS and OS. Better clinical and biologic prognostic factors for failure-free survival after ASCT, as well as refinements in PBSC harvesting and purging methods, should identify which patients with advanced FL are likely to benefit from an autograft, and alternatively which should proceed to other promising therapies under investigation such as allogeneic SCT[20,26,27] monoclonal antibody-targeted therapies or other experimental treatments.[28,29]

Contributions and Acknowledgments

RL designed the study, was responsible for data management and prepared the manuscript. RM performed the data analysis and participated in writing the paper. AS collaborated in patient care and data management. JS is the head of the Clinical Hematology Division and participated in writing the paper, JG is the head of Institut de Recerca Oncològica. JN, JB, GMH and SB collaborated in patient care and in preparation of the manuscript.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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