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Non-Hodgkin's lymphoma

Autologous stem cell transplantation for clinically aggressive non-Hodgkin's lymphoma: the role of preparative regimens

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Summary:

We investigated the impact of the most commonly used preparative regimens on the outcome of 395 patients with diffuse large cell lymphoma (DLCL), consecutively reported to the registry of the Spanish GEL/TAMO. Among them, 139 (35%) were autografted in 1st CR, 86 (22%) in 2nd/3rd CR, 124 (31%) had chemosensitive disease and 46 (12%) had chemoresistant disease. Conditioning consisted of chemotherapy-only in 348 patients (BEAM, 164; BEAC, 145; and CBV, 39) and radiochemotherapy with CY and TBI in 47. Median times to granulocyte, platelet recovery and to discharge were significantly shorter in the chemotherapy-only group. Early transplant-related mortality was significantly higher when using CY-TBI. After a median follow-up of 28 months, overall survival (OS) at 8 years of patients conditioned with BEAM or BEAC (58% (95% CI 50–66%)) was more favorable than with CBV (40% (95% CI 24–56%)), and significantly better than with CY-TBI (31% (95% CI 18–44%)). Multivariate analysis revealed that patients conditioned with chemotherapy-only regimens had improved OS, disease-free (DFS) and relapse-free survival (RFS) when compared to those conditioned with CY-TBI. Status at transplant was also a powerful prognostic indicator. We conclude that preparative regimens consisting of chemotherapy-only seem more efficacious than CY-TBI as conditioning for DLCL, because of faster engraftment and greater antilymphoma effect, as indicated by improved OS, DFS and RFS. *Bone Marrow Transplantation* (2001) **27,** 405–412.
Keywords: high-dose therapy; preparative regimens; non-Hodgkin's lymphoma; prognostic factors; diffuse large cell lymphoma

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Over the past two decades, high-dose therapy (HDT) followed by autologous stem-cell transplantation (ASCT) has been explored to improve the long-term outcome of patients with non-Hodgkin's lymphoma (NHL). Despite the many reports, a number of questions remain unanswered regarding the best transplantation technique in this spectrum of disorders.[1–5]

In this study we focused on the diffuse large cell lymphomas (DLCL), a category mainly represented by centroblastic and immunoblastic lymphomas[6–8] (groups G and H of the Working Formulation[9]). These lymphomas have rapid clinical aggressiveness and despite the use of doxorubicin-containing regimens, up to 50% of cases either fail to achieve an initial complete remission or subsequently relapse.[10–12] In patients with high-risk factors for failure on first-line therapy and in those who relapse, conventional chemotherapy regimens result in less than 20% 2-year disease-free survival in most series.[13–15] ASCT has been widely used to improve the outcome in these patients.[15–37] Status at transplant and sensitivity to conventional chemotherapy have been consistently identified as prognostic factors for survival. In contrast, impact of the conditioning regimen is a controversial matter. Multiple HDT regimens using chemotherapy-only or in combination with total body irradiation (TBI) have been explored, but to date neither has been found clearly superior.[21–26,38–39]

To investigate the impact of the most commonly used preparative regimens on engraftment, toxicity and disease outcome after ASCT for DLCL, we analyzed 395 patients autografted in 35 Spanish hospitals. All these patients were prospectively reported to the registry of the Spanish GEL/TAMO Cooperative Group for Bone Marrow Transplantation in Lymphomas.

Patients and methods

Patient characteristics at diagnosis

Between June 1983 and March 1999, 395 consecutive patients with clinically aggressive NHL belonging to the G and H categories according to the Working Formulation[9] for clinical usage were autografted at 35 Spanish hospitals. Data were registered at the GEL/TAMO Statistical Center. Patient characteristics at diagnosis are shown in Table 1. Several chemotherapy regimens had been used as front-line treatment. Two-hundred and seven patients (52%) had been treated with CHOP, 78 (20%) with MACOP-B, 54 (14%) with ProMACE-CytaBOM and 56 (14%) with other doxorubicin-containing regimens. Tumor response to first-line therapy had been complete remission (CR) in 271 patients (68%), partial remission (PR) in 90 (23%) and failure in 34 (9%). Of the patients who had achieved CR, 88% had received one regimen as initial therapy and 12% two or more consecutive regimens. Forty-four percent of patients who had achieved initial CR had relapsed before ASCT. Patients who had not achieved CR and those who relapsed had been treated with salvage chemotherapy regimens. These regimens varied among centers.

Patient characteristics at autologous transplantation

Disease status at the time of HDT and ASCT was: first CR in 139 patients (35%), second CR in 78 (20%), third CR in eight (2%), chemosensitive disease (SD) in 124 (31%) and chemoresistant disease (RD) in 46 (12%). Patient characteristics at autologous transplantation are summarized in Table 1. Median interval between diagnosis and transplantation was 10 months (range, 2–632). Of the 139 patients who were autografted in first remission, distribution according to the International Prognostic Index[40] (IPI) at diagnosis was as follows: 35 patients (25%) low risk, 36 (26%) low–intermediate risk, 27 (19%) intermediate–high risk, 29 (21%) high risk and 12 (9%) unknown. Patient characteristics according to the preparative regimen are listed in Table 2.

Table 1 Patient characteristics at diagnosis and at autologous transplantation

	Diagnosis	*Autologous transplantation*
Median age (years) (range)		42 (4–75)
Sex (male/female)	226/169	
B symptoms (%)	190 (48)	21 (13)
Stage III–IV (%)	282 (71)	82 (49)
Tumor size >10 cm (%)	216 (55)	19 (5)
Bone marrow involvement (%)	88 (22)	15 (4)
No. extranodal sites ⩾2 (%)	124 (31)	18 (5)
Performance status (ECOG ⩾2) (%)	155 (38)	20 (5)
LDH level (>1 nv) (%)	218 (62)	45 (12)
β2-microglobulin (>1 nv) (%)	96 (49)	49 (30)
IPI (%)		
0–1	119 (30)	332 (84)
2	99 (25)	34 (9)
3	75 (19)	19 (4)
4–5	57 (15)	2 (1)
Unknown	45 (11)	8 (2)

IPI = International Prognostic Index; nv = normal value.

Hematopoietic stem cells

Bone marrow was harvested in 152 patients, and treated *ex vivo* with monoclonal antibodies and complement in eight cases. Median number of mononucleated cells (MNC) was 1.7×10^8/kg (range, 0.3–5.8). In 243 patients, stem cell progenitors were collected from peripheral blood (previously harvested bone marrow was also infused in 48 patients). Growth factors (G- or GM-CSF) were used as mobilizing agents in 116 patients and chemotherapy followed by growth factors in 74 cases. Median number of $CD34^+$ cells collected was 3.4×10^6/kg (range, 1.0–50.9).

High-dose therapy regimen and transplantation procedures

Preparative regimens varied according to the participating centers. Forty-seven patients received radiochemotherapy consisting of cyclophosphamide (60 mg/kg for 2 consecutive days) and TBI (9–12 Gy in one to four fractions) (CY-TBI).[18,21,24] The remaining 348 patients were treated with chemotherapy-only: BEAM[20,41,42] (164 patients), BEAC[14,25] (145 patients) and CBV[26,30,43] (39 patients). Isolation procedures, prophylactic antibiotic therapy and blood component management have been reviewed elsewhere.[27] Colony-stimulating factors were used to stimulate hematological recovery in 273 patients (69%).

Study definitions

CR was defined as the disappearance of all clinical evidence of the disease with normalization of X-rays, CT scans and laboratory values that had been abnormal before therapy. PR and sensitive relapse were defined as a reduction of ⩾50% in measurable disease for at least 1 month. Patients were defined as being in resistant relapse if their lymphoma progressed through their initial combination chemotherapy treatment or if their disease responded less than a PR to salvage therapy. Overall survival (OS) was defined as the time from the day of autologous transplant until death from any cause or last date known alive. Disease-free survival (DFS) was defined as time from the day of autologous transplant until relapse, death from any cause or last date known alive. Relapse was evaluated in patients autografted in CR and in those who achieved CR with HDT (relapse-free survival, RFS).

Statistical methods

The chi-square test, Fisher's exact test and logistic regression analysis were used for comparison between groups. Comparison of continuous variables was performed by linear regression analysis. Actuarial curves of DFS, RFS and OS were performed according to the Kaplan–Meier method[44] and comparison between curves was performed using the log-rank test.[45] The factors examined to have impact on outcome were the following: period of transplant (1983–1993 *vs* 1994–1999), age (⩽60 *vs* >60), sex, histology (group G *vs* H), phenotype (B *vs* T), response to first-line therapy (RC *vs* RP *vs* failure), disease status at transplant (1st CR *vs* 2nd/3rd CR *vs* SD *vs* RD), ECOG at

Table 2 Patient characteristics at autologous transplantation according to the preparative regimen

	CY-TBI	*BEAM*	*BEAC*	*CBV*	*P*
Age >60 years (%)	3 (6)	9 (5)	11 (8)	3 (8)	NS
Sex, male (%)	22 (47)	92 (56)	84 (56)	28 (71)	NS
Centroblastic histology (%)	23 (49)	138 (81)	103 (71)	32 (82)	<0.001
B phenotype (%)	24 (83)	103 (78)	94 (82)	25 (89)	NS
CR after first-line therapy (%)	32 (71)	110 (67)	103 (71)	26 (67)	NS
Transplant after 1994 (%)	13 (38)	35 (79)	100 (69)	20 (51)	0.001
Peripheral blood stem cells (%)	13 (38)	114 (70)	88 (61)	28 (72)	0.001
B symptoms (%)	6 (9)	9 (13)	5 (8)	2 (11)	NS
Tumor size >10 cm (%)	2 (4)	8 (5)	7 (5)	2 (5)	NS
Bone marrow involvement (%)	2 (4)	8 (5)	5 (4)	0	NS
No. extranodal sites ⩾2 (%)	2 (4)	7 (5)	5 (4)	2 (5)	NS
ECOG ⩾2 (%)	5 (11)	8 (5)	5 (4)	2 (5)	NS
LDH level (>1 nv) (%)	10 (24)	16 (10)	15 (11)	4 (10)	NS
Status at transplant (%)					
1st CR	19 (40)	60 (37)	50 (35)	10 (26)	<0.01
2nd/3rd CR	7 (15)	34 (21)	34 (23)	11 (28)	
Chemosensitive disease	8 (17)	53 (32)	51 (35)	12 (31)	
Chemoresistant disease	13 (28)	17 (10)	10 (7)	6 (15)	
IPI (%)					
0–1	32 (68)	147 (90)	121 (83)	32 (82)	NS
2	6 (13)	10 (6)	14 (10)	4 (10)	
3	6 (13)	6 (4)	6 (4)	1 (3)	
4–5	1 (2)	0	1 (0)	0	
Unknown	2 (4)	1 (0)	3 (2)	2 (5)	

CY-TBI = cyclophosphamide and total body irradiation; nv = normal value; CR = complete remission; IPI = International Prognostic Index; NS = not significant.

transplant (0.1 *vs* ⩾2), LDH at transplant (<1 *vs* ⩾2 normal value), number of extranodal sites (<1 *vs* ⩾2), tumor size (<9 cm *vs* ⩾10 cm), stage (I-II *vs* III–IV), preparative regimen (BEAM, BEAC, CBV, CY-TBI), source of stem cells (bone marrow *vs* peripheral blood stem cells), use of growth factors after transplant. Variables found to be associated with DFS, RFS or OS on univariate analyses were entered into a multivariate analysis. Multivariate analysis of prognostic factors was performed according to the Cox model of multiple regression.[46] All *P*-values are two-sided and statistical significance was defined as a $P < 0.05$.

Results

Hematological recovery

Eight patients (2%) died early after transplant and were not evaluable for engraftment. A granulocyte count above 0.5×10^9/l and a stable platelet count above 20×10^9/l were attained after a median of 12 days (range, 8–135) and 15 days (range, 7–175), respectively. Median time to discharge was 20 days (range, 9–181). Median time to granulocyte recovery was 14 days in the CY-TBI group (range, 8–51) and 12 days in the chemotherapy-only group (range, 8–135). This difference was statistically significant ($P = 0.003$). Platelet recovery was achieved at a median of 20 days in the CY-TBI group (range, 7–129) and 14 days in the chemotherapy-only group (range, 7–175) ($P = 0.017$). The median time to discharge was significantly different between patients in the CY-TBI *vs* the chemotherapy-only group, with a median time of 25 days (range, 11–77) and 19 days (range, 9–181), respectively ($P = 0.004$). Table 3 summarizes data on hematological recovery with each preparative regimen. Recovery of granulocytes (11 (8–135) days *vs* 16 (8–51) days, $P < 0.0001$) and platelets (13 (7–175) days *vs* 20 (7–129) days, $P < 0.0001$) was significantly faster for patients autografted with peripheral blood stem cells compared to bone marrow. Granulocyte recovery was also faster when using growth factors (12 days (8–51) *vs* 14 days (9–135), $P < 0.0001$). On multivariate analysis, the use of peripheral blood as a stem cell source remained significant for both granulocyte ($P < 0.0001$) and platelet ($P < 0.0001$) recovery, and the use of growth factors for granulocyte recovery ($P < 0.01$).

Toxicity

Sepsis or pneumonia developed in 171 patients (43%) and fungal infection in 18 (5%). Interstitial pneumonitis was documented in 15 patients (4%), cardiac toxicity in 12

Table 3 Hematological recovery among groups

	Granulocytes $>0.5 \times 10^9/l$	*Platelets* $>20 \times 10^9/l$	*Discharge*
CY-TBI	14 (8–51)[a]	20 (7–129)[a]	25 (11–77)[a]
BEAM	12 (8–135)	15 (7–175)	21 (9–181)
BEAC	12 (8–38)	14 (7–77)	18 (11–72)
CBV	12 (9–51)	15 (9–51)	21 (12–51)

Median days (range).
CY-TBI = cyclophosphamide and total body irradiation.
[a]$P < 0.05$.

(3%), severe bleeding in three (1%), hemorrhagic cystitis in five (1%) and liver veno-occlusive disease in five (1%). There were no statistically significant differences in acute toxicity between the CY-TBI and the chemotherapy-only group.

Thirty-two (8.1%) patients died early (within the first 100 days) due to transplant-related complications. Causes of early transplant related mortality (TRM) are shown in Table 4. In univariate analysis, TBI regimen ($P = 0.05$), bone marrow as a stem cell source ($P = 0.04$) and transplant before 1994 ($P = 0.0007$) were associated with statistically higher TRM. Multivariate analysis identified transplant before 1994 as a significant prognostic factor for early TRM (RR 4.7 95% CI 1.55–14.23, $P < 0.006$).

Mortality from transplant-related causes beyond 100 days has been reported in nine patients: three with secondary malignancy, two myelodysplasia, one liver dysfunction, one interstitial pneumonia and two not specified.

Disease response

Response to transplant was evaluated 3 months after the procedure. Twelve patients (3%) were not evaluable due to early death. All patients autografted in CR retained this status at 3 months. Ninety-two (74%) patients with SD at transplant and six (13%) of those with RD reached a CR after conditioning. In patients autografted with disease, multivariate regression analysis revealed that chemosensitivity before transplant was a significant prognostic factor for response (RR 2.97 95% CI 7.35–51.45, $P = 0.0001$).

At last follow-up, 87 of the 323 patients in CR after transplant had relapsed at a median of 6 months (3–70 months). Thirteen patients (40%) of those conditioned with CY-TBI and 74 (26%) from the chemotherapy-only group ($P = 0.09$) relapsed.

Prognostic factors for OS

After a median follow-up of 28 months for survivors, the predicted 8-year OS was 51% (95% CI 46–56%) and the median OS had not been reached (Figure 1). Univariate analysis identified factors predicting survival: period of transplant, response to first-line therapy, number of first-line regimens, status at transplant, conditioning, B symptoms, ECOG, LDH, number of extranodal sites, tumor size and stage. On multivariate analysis, the use of chemotherapy-only as a preparative regimen and disease status at transplant were factors associated with a significantly higher probability of survival ($P = 0.0007$ and $P = 0.00005$, respectively) (Table 5). In this series, OS at 8 years of patients conditioned with BEAM or BEAC (58% (95% CI 50–66%)) was more favorable than with CBV (40% (95% CI 24–56%)), and significantly better than with CY-TBI (31% (95% CI 18–44%)). Patients autografted in first CR had improved OS at 8 years (69% (95% CI 62–77%)) than those in 2nd/3rd CR or SD (54% (95% CI 44–64%) and 54% (95% CI 45–63%), respectively). The poorest outcome was for those patients autografted in RD (33% (95% CI 20–46%)). After adjustment, the prognostic value of conditioning and disease status is shown in Figure 2.

For patients in first CR, OS at 8 years was similar between BEAM and CBV (82% (95% CI 74–90%) and 89% (95% CI 78–100%), respectively), and significantly worse with the CY-TBI regimen (46% (95% CI 24–68%)) ($P = 0.03$).

Table 4 Causes of early toxic death

	CY-TBI	*Chemotherapy-only*
Sepsis/pneumonia (%)	3 (6.4)	5 (1.4)
Fungal infection (%)		3 (0.9)
Other infection (%)		2 (0.6)
Respiratory distress (%)		4 (1.2)
Multi-organ failure (%)		1 (0.3)
Severe bleeding (%)	2 (4.2)	4 (1.2)
Interstitial pneumonitis (%)		1 (0.3)
Liver VOD (%)	1 (2.1)	1 (0.3)
Cardiac toxicity (%)	1 (2.1)	3 (0.9)
Other (%)		1 (0.3)
Total (%)	7 (14.8)	25 (7.4)

CY-TBI = cyclophosphamide and total body irradiation; VOD = veno-occlusive disease.

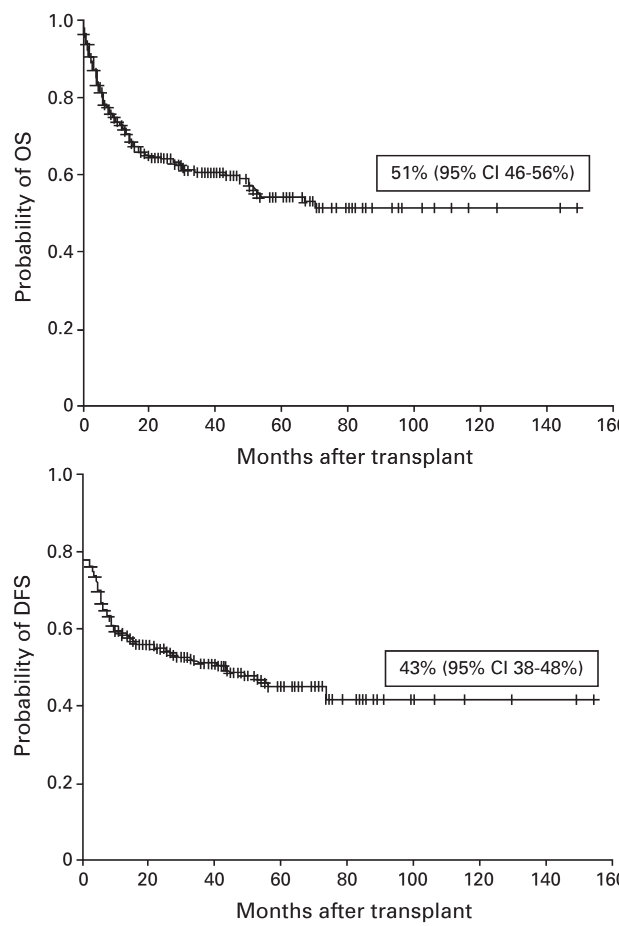

Figure 1 Overall survival (OS) and disease-free survival (DFS) for the whole series ($n = 395$ patients).

Table 5 Multivariate regression analysis of prognostic factors

	RR	*95% CI*	*P*
Prognostic factors for OS			
Conditioning			
BEAM	1		
BEAC	1.33	0.87–2.02	0.18
CBV	1.30	0.74–2.28	0.36
CY-TBI	2.81	1.72–4.61	0.00005
Status at transplant			
1st CR	1		
2nd/3rd CR	2.32	1.37–3.94	0.002
Stable disease	2.35	1.43–3.87	0.0008
Refractory disease	13.21	7.74–22.54	0.00005
Prognostic factors for DFS			
Conditioning			
BEAM	1		
BEAC	0.96	0.67–1.38	0.85
CBV	1.26	0.77–2.05	0.34
CY-TBI	1.74	1.09–2.66	0.02
Status at transplant			
1st CR	1		
2nd/3rd CR	2.12	1.34–3.36	0.001
Stable disease	2.48	1.61–3.8	0.00005
Refractory disease	10.20	6.27–16.58	0.00005
Prognostic factors for RFS			
Conditioning			
BEAM	1		
BEAC	1	0.64–1.55	0.99
CBV	1.43	0.78–2.65	0.24
CY-TBI	2.04	1.15–3.61	0.01
Status at transplant			
1st CR	1		
2nd/3rd CR	2.30	1.45–3.65	0.0004
Stable disease	1.42	0.87–2.33	0.15
Refractory disease	4.27	1.64–11.09	0.003

RR = relative risk; CI = confidence interval; OS = overall survival; DFS = disease-free survival; RFS = relapse-free survival; CR = complete remission; CY-TBI = cyclophosphamide and total body irradiation.

Prognostic factors for DFS

DFS at 8 years was 43% (95% CI 38–48%) (Figure 1). Period of transplant, response to first-line therapy, number of first-line regimens, status at transplant, conditioning, B symptoms, ECOG, LDH, number of extranodal sites, tumor size and stage correlated with DFS in the univariate analysis. According to the Cox model, the probability of DFS was significantly better in the group of patients conditioned with chemotherapy-only than in patients treated with CY-TBI. Status at transplant was also predictive (Table 5 and Figure 2).

Prognostic factors for RFS

The median RFS was 97 months. We found that period of transplant, status at transplant, conditioning and LDH had statistically significant prognostic value for RFS in the univariate analysis. Use of chemotherapy-only as a preparative regimen (and especially with BEAM or BEAC) was associated with a lower probability of relapse than CY-TBI. Another predictive factor for RFS in multivariate analysis was status at transplant (Table 5 and Figure 2).

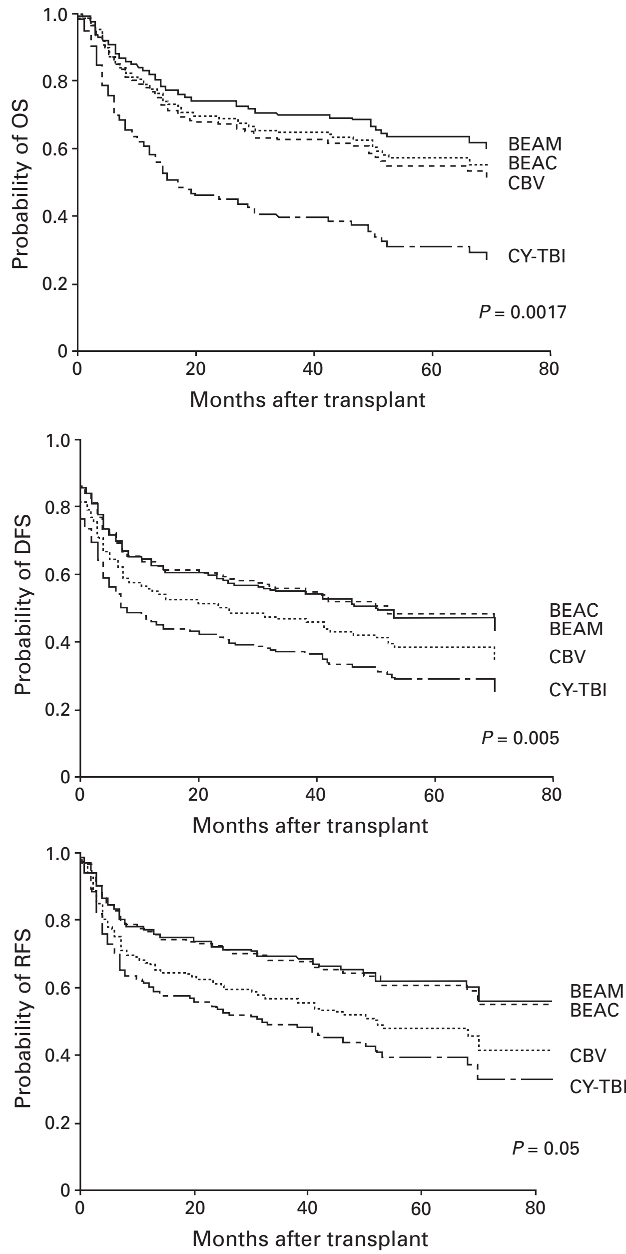

Figure 2 Adjusted overall survival (OS), disease-free survival (DFS) and relapse-free survival (RFS) according to the preparative regimen. BEAM, 194 patients; BEAC, 145 patients; CBV, 39 patients; CY-TBI (cyclophosphamide and total body irradiation), 47 patients.

Discussion

During the last two decades, high-dose therapy followed by autologous stem-cell transplantation have been extensively used in patients with aggressive NHL.[1–5] Various schedules including chemotherapy-only or in combination with TBI have been administered as conditioning for transplantation.[15–37] It remains unclear which regimen is superior.[21–26,38,39] In an attempt to clarify this question we investigated the prognostic value of the main preparative regimens in a group of 395 patients with diffuse large cell lymphoma consecutively reported to the registry of the GEL/TAMO Cooperative Group.

Our results confirmed that ASCT produces prolonged DFS and OS in a substantial proportion of patients with clinically aggressive NHL. The preparatory regimens based on a combination of drugs significantly correlated with a better outcome in terms of OS, DFS and RFS compared to CY-TBI. In this last group, a higher proportion of patients received transplantation before 1994, as well as bone marrow rescue instead of peripheral stem cells. Neither period of transplantation nor source of stem cells resulted in major differences in outcome. On multivariate analysis, when other potentially confounding factors were analyzed, impact of the preparative regimen on outcome remained significant. Other reports on HDT and ASCT for NHL have also compared chemotherapy-only to TBI-based regimens.[21–26] In contrast to this report, such studies were usually performed on small series of patients with several NHL categories and with various dose-intensity programs. No significant differences in survival between the two modalities were detected in these studies, although the above-mentioned limitations may account for these findings.[39]

In the present study, we found a similar complete response rate among the regimens tested with a RFS advantage in patients receiving chemotherapy-only. This was mainly due to a higher relapse rate in the group of patients treated with chemoradiotherapy. In other series,[21–27] similar relapse rates were obtained using regimens with or without TBI, but these studies included patients with indolent lymphomas which are classically associated with greater sensitivity to irradiation than is aggressive HNL.

Among the chemotherapy combinations used in our study, the BEAM and BEAC regimens appeared equivalent in terms of efficacy and outcome, with similar DFS, RFS and OS. The survival curves obtained with the CBV regimen were lower, but not statistically different when compared with the two other non-containing-TBI regimens. An important advantage of using chemotherapy-only regimens is the possibility of administering involved-field radiotherapy, although it is controversial whether this should be applied before or after HDT.

Toxicity and mortality following transplantation are an important issue. The high anti-neoplasic effect of the high-dose regimen may be offset by transplant-related mortality. TRM has decreased in recent years because of improvements in supportive care, the current use of PBSC and refinements in patient selection. Nevertheless, the rate remained at 7% in the most recent report of the EBMT registry.[47] The slightly higher TRM rate observed in our series (10%) may be explained by the inclusion of a significant number of patients with refractory disease and who were heavily pretreated. These two factors are well-correlated with a high early TRM. Acute toxicity and early TRM were similar among the conditioning regimens compared here, and the use of a TBI-containing regimen was not associated with increased pulmonary toxicity, as previously reported in other series.

Regarding hematologic toxicity, engraftment was prompt in most patients. Patients conditioned with the TBI regimen had a significantly delayed granulocyte and platelet recovery compared to patients treated with chemotherapy-only. This fact may be due to higher stromal cell damage when using radiotherapy. Interactions between progenitor cells and stromal cells are necessary for providing adequate function of the bone marrow microenvironment and, therefore, ordered production of mature blood elements. In addition, time to discharge was significantly longer in the TBI group. It could be argued that the prolonged myeloablative effect of the TBI regimen should be associated with better outcome due to a greater anti-lymphoma activity. However, in this series the most efficacious regimens were BEAM and BEAC, and both were related to a lower hematologic toxicity, which suggests anti-lymphoma activity is not necessarily related to hematologic toxicity.

In recent years, late complications of transplants, including MDS and acute leukemia, have attracted considerable interest.[48–54] Initial reports from single institutions have shown an unexpectedly high incidence of these complications (14–18% after 5 to 6 years following ASCT). Several factors have been associated with this finding: age over 35–40 years, use of TBI, use of PBSC, duration of previous therapy, prior extensive use of alkylating agents and pelvic irradiation. Recently, the EBMT[54] has reported a lower rate of MDS/acute leukemia than in previous studies, with an actuarial risk of 3% (2.0–4.3 95% CI) at 5 years post-transplant for NHL. Furthermore, the EBMT identified age, radiotherapy, number of transplants, and interval between diagnosis and transplant as risk factors for this complication. The low rate seen in our series may be explained by the fact that we excluded patients with low-grade NHL, a group which is possibly more likely to suffer this complication. This occurred in 7.5% (4.5–12.3 95% CI) of patients at 5 years compared to 1.2% (0.6–2.3 95% CI) in intermediate/high-grade NHL. The higher MDS/leukemia risk for patients with low-grade disease may be influenced by the more prolonged use of low-dose alkylating agents and the use of fludarabine.

Other studies in patients with aggressive lymphoma treated with ASCT have shown that the strongest prognostic factor for outcome is the status of the disease prior to transplantation.[18–30] In our series, the predicted overall survival of patients in first CR was 69% at 8 years and 54% for those autografted in second or later CR. These figures are similar to those reported by other groups. IPI at diagnosis identified patients with a different outcome following transplantation.[55] The IPI score may also be useful for identifying patients who may benefit from ASCT as consolidation therapy in first CR. Recently published reports suggest an improved outcome with this approach in patients with high risk factors at diagnosis.[31–37]

In the present study, patients with chemosensitive-relapse achieved a CR of 74% with a DFS and OS of 39% and 44% at 8 years, respectively. These figures are similar to previously reported data.[18–30] A considerable number of patients therefore still relapse after transplantation. The PARMA study has recently demonstrated that the time to relapse is of prognostic value. Patients relapsing early had a poor outcome with a PFS of 8% at 8 years.[56] Our data regarding patients autografted with refractory disease are also poor. The OS of 6% at 8 years found in this study is comparable to other series, and advises against carrying out autologous transplants in this setting. In consequence, alternative approaches need to be tested in order to improve outcome in patients with early relapse or resistant disease.

In summary, the data in this study indicate that in patients with diffuse large cell lymphomas chemotherapy-only conditioning regimens seem more efficacious than CY-TBI. More rapid engraftment and greater anti-lymphoma activity (as indicated by a better RFS, DFS and OS) are expected with BEAM or BEAC combinations. Because of the lack of a randomized trial analyzing the value of the preparative regimens in aggressive NHL, the study herein presented is of particular interest. According to these findings, we recommend BEAM or BEAC as the standard preparative regimens for conditioning in patients with diffuse large cell lymphoma.

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