Impact of the use of autologous stem cell transplantation at first relapse both in naïve and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study

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ABSTRACT

Background
We analyzed detailed characteristics and salvage treatment in 175 follicular lymphoma patients from the FL2000 study who were in progression after first-line therapy with or without addition of rituximab to chemotherapy and interferon.

Design and Methods
The impact of using autologous stem cell transplantation and/or rituximab administration at first progression was investigated, taking into account initial therapy. With a median follow up of 31 months, 3-year event free and overall survival rates after progression were 50% (95%CI 42-58%) and 72% (95%CI 64-78%), respectively.

Results
The 3-year event free rate of rituximab re-treated patients (n=112) was 52% (95%CI 41-62%) *versus* 40% (95%CI 24-55%) for those not receiving rituximab second line (n=53) (*P*=0.075). There was a significant difference in 3-year overall survival between patients receiving autologous stem cell transplantation and those not: 92% (95%CI 78-97%) *versus* 63% (95%CI 51-72%) (*P*=0.0003), respectively. In multivariate analysis, both autologous stem cell transplantation and period of progression/relapse affected event free and overall survival.

Conclusions
Regardless of front-line rituximab exposure, this study supports incorporating autologous stem cell transplantation in the therapeutic approach at first relapse for follicular lymphoma patients.

Key words: follicular lymphoma, autologous stem cell transplantation, rituximab.

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Introduction

Follicular lymphoma (FL) is an indolent B-cell hematologic malignancy. Prognosis for patients with FL has significantly improved during the last decade.[1,2] Addition of rituximab to conventional chemotherapy has brought a significant development, with four phase III randomized trials proving a benefit in favor of a rituximab-containing chemotherapy up front.[3-6] Among these trials, the FL2000 trial showed that 6 courses of CHVP plus rituximab and interferon-α2a (R-CHVP-I) provided superior disease control than 12 courses of CHVP plus interferon-α2a (CHVP-I) for untreated FL with high tumor burden. The results of the FL2000 trial have recently been published with a median 5-year follow up.

In spite of better event free survival (EFS) in the R-CHVP-I arm, no plateau was observed on the EFS curve in any arm, reflecting a continuing relapse rate. It also remains unknown, in spite of some studies,[7,8] whether re-treatment with rituximab can be efficient in patients who have already received immunochemotherapy.

Since the late 80s, the role of high-dose chemotherapy followed by autologous stem cell transplantation (HDC-ASCT) in FL treatment has been questioned. Several studies suggested a clinical benefit when performed after first-line treatment failure.[9-11] Furthermore, there is proof that some patients reach a complete response (CR), including molecular remission, after HDC-ASCT.[12]

In the rituximab era, the best second-line treatment in FL, and the role of both HDC-ASCT and re-treatment with rituximab, remain of major interest. To address this issue, we analyzed the outcome of relapsed/refractory patients in the FL2000 trial, evaluating the use of HDC-ASCT and rituximab, while specifically considering the impact of the patients' initial therapy.

Design and Methods

Patient selection

The FL2000 trial was a collaborative study of the GELA and the GOELAMS groups. It was a prospective, multicenter, open, randomized phase III trial comparing R-CHVP-I and CHVP-I as first-line treatments in FL patients. Patients' characteristics, inclusion criteria and study design have been recently published.[6] Briefly, untreated high tumor burden FL patients were randomly assigned to receive either 12 CHVP courses (cyclophosphamide, doxorubicin, etoposide and prednisolone), i.e. both induction and consolidation courses plus interferon-α2a over 18 months (CHVP-I), or 6-monthly CHVP courses plus interferon-α2a combined with 6 rituximab infusions (R-CHVP-I). Hence, the arms were distinguished by the use or not of rituximab during induction instead of consolidation chemotherapy.

Although there was a reduction in the number of chemotherapy courses in the R-CHVP-I arm, final analysis proved that the addition of rituximab gave a superior disease control than the 12 CHVP-I courses. The 5-year EFS rate estimates were 53% *vs.* 37% (P=0.0004). However, no significant difference was observed in overall survival (OS), suggesting that second-line treatment may be important for patients whose first-line therapy failed. In the FL2000 study, the choice of therapeutic strategy at first progression or relapse was left to the local physician. All relapsed or refractory FL2000 patients were eligible for the present study.

The protocol was approved by the local or national ethics committees and the national regulatory agency according to French and Belgium law.

Methods

As planned in the FL2000 protocol, local investigators reported data concerning the date and site(s) of progression or relapse, the histological transformation and the type of second-line treatment (immunotherapy i.e. rituximab or other agents, salvage chemotherapy regimen or HDC-ASCT).

Statistical analysis

Overall survival and event-free survival probabilities were calculated using Kaplan-Meier estimates. Patient outcome was censored at the last contact date. Overall survival (OS) was estimated from the date of relapse or progression until death, whatever the cause. EFS was estimated from the date of first relapse or progression until death (whatever the cause), second progression/relapse or last follow up. The log rank test was used for univariate comparisons. Factors having potential prognostic significance in univariate analysis were: initial randomization arm in the FL2000 trial (CHVP-I *vs.* R-CHVP-I); relapse or progression period (while on therapy or after completion of chemo œtherapy); FLIPI score at diagnosis; age at the time of progression; sex; type of salvage chemotherapy regimen (cytarabine-, alkylating-, anthracycline- or fludarabine-based regimen); the use of rituximab at first relapse (patients receiving an immunotherapy-containing treatment other than rituximab at first relapse were excluded) (n=10); and HDC-ASCT. When analyzing the impact of HDC-ASCT according to front-line treatment, patients over 70 years of age were excluded in order to reduce age bias (n=22). Variables found to be statistically significant at the P<0.2 level in univariate analysis were included in the multivariate analysis. For multivariate analysis, P<0.05 was considered significant. The proportional hazard assumption was tested for all factors. Statistical analysis was performed using SAS software, version 9.1.

Results

Patients' characteristics and salvage therapies

Three hundred and fifty-eight patients were included in the FL2000 trial. A total of 175 patients presenting with confirmed FL (after central pathological review) experienced relapse or progression (Table 1). Data from all the 175 refractory/relapsed patients were analyzed. One hundred and five patients were initially randomized in the CHVP-I arm and 70 in the R-CHVP-I arm. At time of first progression, histological analysis on biopsy was performed in 105 cases and histological transformation (HT) was diagnosed in 14 cases (8 in the CHVP-I arm and 6 in the R-CHVP-I arm).

At diagnosis, the FLIPI score was low in 24 cases, intermediate in 51 and high in 95 (data missing in 5). First progression occurred in an initially involved site in 37% of the cases. At that time, median age was 60 years (range 25-75 years). Median time from diagnosis to progression was 2.8 years (range 1.47-5.65 years). Sixty-three patients progressed on therapy (37 during induction and 26 during consolidation chemotherapy) while 112 patients progressed after completion of first-line treatment.

Various chemotherapy regimens were administrated (Table 1). Sixty-three patients (including 28 out of the 105 patients initially randomized in the CHVP-I arm) did not receive rituximab at first relapse. Other monoclonal anti-

Table 1. Detailed characteristics of the 175 patients according to front-line treatment.

	Total	CHVP+I	R-CHVP-I	*P* value
Number	175	105	70	
Male/Female	85/90	45/60	40/30	0.06
Median age	60 (25-75)	60 (28-75)	59 (25-74)	0.17
FLIPI score at diagnosis (missing=5)				0.6
0-1	24	14	10	
2	51	28	23	
3-5	95	60	35	
Relapse period				0.6
Induction phase	37	24 (23%)	13 (19%)	
Consolidation phase	26	17 (16%)	9 (13%)	
Follow-up period	112	64 (61%)	48 (68%)	
Histological transformation	14	8	6	0.8
Chemotherapy regimens at first relapse				
Fludarabine-based	29 (16.5%)	19 (18%)	10 (14%)	0.5
Anthracycline-based	38 (22%)	26 (25%)	12 (17%)	0.23
Cytarabine-based	42 (24%)	25 (24%)	17 (24%)	0.95
Cyclophosphamide-based	40 (23%)	22 (21%)	18 (25%)	0.46
Immunotherapy at first relapse				
Yes	122	81 (77%)	41 (58.5%)	0.009
Containing rituximab	112 (64%)	77 (73%)	35 (50%)	0.004
HDC-ASCT at first relapse	42 (24%)	29 (27.5%)	13 (18.5%)	0.17

FLIPI: Follicular Lymphoma International Prognostic Index; HDC-ASCT: high-dose chemotherapy followed by autologous stem cell transplantation.

bodies administered included: ^{90}Y ibritumomab tiuxetan (n=6), other CD20-targeted monoclonal antibodies (n=3) or anti-CD22 monoclonal antibody (n=1). In total, 122 patients received some form of "immunotherapy-containing" salvage therapy (including 81 of 105 patients who failed CHVP-I and 41 of 70 who failed R-CHVP-I). At first relapse, forty-two patients (24%) proceeded to HDC-ASCT. Among these transplanted patients, 11 patients had progressed during the induction phase, with 4 patients of the R-CHVP-I arm and 7 of the CHVP-I arm, respectively. Median age of transplanted and non-transplanted patients was 50 (range 27-68 years) and 60 years (range 25-69 years) (*P*=0.002), respectively. The most common conditioning regimens were BEAM (carmustine, etoposide, cytarabine and melphalan) (50%) and TBI-cyclophosphamide (26%).

Considering all patients with relapsed or progressive disease, response after completion of second-line therapy was complete remission (CR)/complete unconfirmed remission (Cru) in 80 cases (46%), partial remission (PR) in 23 (13%), less than partial remission (PR) in 37 (21%) (data missing in 14 cases). At the time of analysis, 45 patients experienced a second progression after salvage therapy and 55 patients had died. The cause of death was lymphoma-related in 34 cases, infection-related in 6, myelodysplastic syndrome in 2 non-transplanted patients, solid tumor in 3, encephalopathy in 2, or others (n=8).

Outcome of patients failing first-line therapy

Median follow up calculated from the time of progression or relapse was 31 months (0-64 months). The 3- and 5-year EFS rates were 50% (95%CI 42-58%) and 26% (95%CI 14-39%), respectively. The 3- and 5-year OS rates were 72% (95%CI 64-78%) and 52% (95%CI 36-66%), respectively (Figure 1).

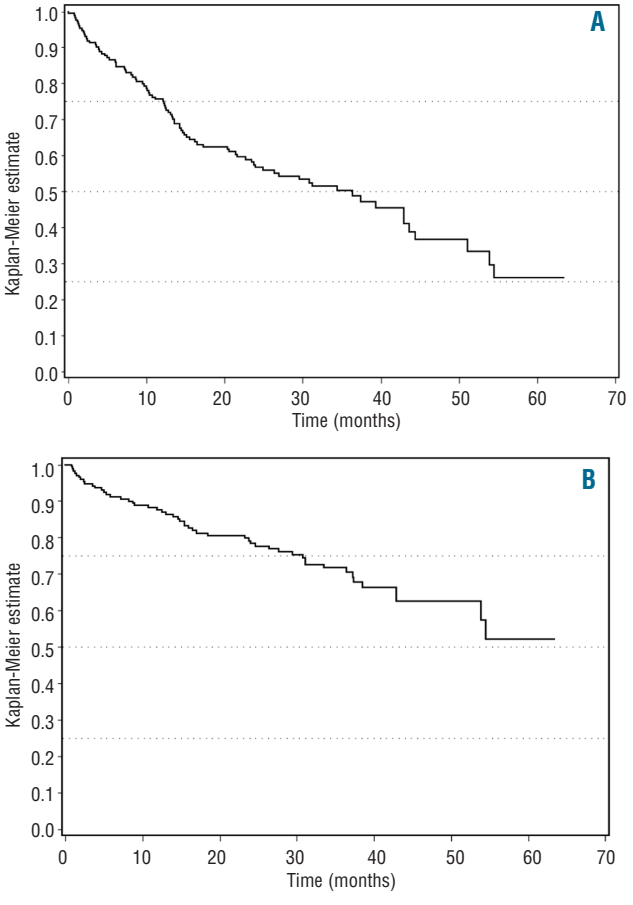

Figure 1. Patient outcome calculated from first progression (n=175). (A) Event-free survival; the 3- and 5-year EFS rates are 50% (95% CI; 42-58%) and 26% (95% CI; 14-39%), respectively. (B) Overall survival; the 3- and 5-year OS rates are 72% (95% CI; 64-78%) and 52% (95% CI; 36-66%), respectively.

Univariate and multivariate analysis for overall survival and event-free survival

For all patients, we analyzed the parameters potentially affecting EFS and OS (Table 2). Univariate analysis showed no statistical difference in EFS and OS according to type of initial therapy (CHVP-I *vs.* R-CHVP-I) and chemotherapy at first progression. There was a non-significant trend for longer EFS when an immunotherapy-containing regimen was used to treat first progression (*P*=0.077). The parameters influencing both EFS and OS were: age at first disease progression; period of disease progression (during induction or consolidation *vs.* after treatment completion); transplantation as first salvage treatment; FLIPI score at diagnosis (0-1 *vs.* 2, 3 or more) and histological transformation (yes *vs.* no). Similar results were observed when the univariate analysis was restricted to patients eligible for transplantation (< or = 70 years).

Histological transformation was not included in the multivariate analysis as this had not been systematically documented. According to this analysis, the parameters that significantly improved EFS were: progression period and transplantation as salvage treatment. Regarding the subgroup of patients that were potentially eligible for transplantation (with an age under 70 years), only these last two parameters remained statistically significant.

Considering OS for all patients, only two parameters remained significant: patients progressing on therapy had a poorer OS; while transplantation used in first salvage treatment improved OS (Figures 2A and 2B). Regarding the subgroup of patients that were eligible for transplantation, these last two parameters, as well as age at relapse (*P*=0.02) were also statistically significant.

Impact of rituximab at first progression according to front-line therapy

To reduce bias, patients receiving immunotherapy other than rituximab were removed from this analysis (n=10). The 3-year EFS rate of patients receiving rituximab (n=112) at first progression was 52% (95%CI, 41-62%) *vs.* 40% (95%CI, 24-55%) for those who did not (n=53) (*P*=0.075). Patient outcome according to previous use of rituximab up front and at first progression were then analyzed. Patients were divided into four subgroups according to when they received rituximab: up front and at first progression (n=35), up front but not at first progression (n=29), not up front but at first progression (n=77), and neither up front nor at first progression (n=24). There was a trend of better 3-year EFS rates for rituximab-naïve patients receiving rituximab at first relapse (n=77) *vs.* rituximab-naïve patients not receiving rituximab at first relapse (n=24) (46% *vs.* 35%; *P*=0.1). The use of rituximab at relapse made no significant difference to 3-year overall survival.

Impact of HDC-ASCT as part of therapy at disease progression

To reduce bias, patients not eligible for transplantation because of age at first progression (>70 years) were removed from this analysis (n=22). Transplanted and non-transplanted patients show different profiles (Table 3): transplanted patients were younger than non-transplanted patients and thus a difference between the two populations regarding FLIPI score at diagnosis was also observed. In addition, transplanted patients more frequently received rituximab at first relapse but their relapse occurred earlier after the first-line treatment. The 3-year survival rates were in favor of patients who underwent HDC-ASCT (n=42). The EFS rate was 73% (95%CI 56-84%) with HDC-ASCT *vs.* 39% (95%CI 29-50%) without (*P*=0.005). Likewise, the OS rate was 92% with HDC-ASCT (95%CI 78-97%) *vs.* 63% without (95%CI 51-72%) (*P*=0.0003).

According to first-line treatment

Patient outcome according to the use of HDC-ASCT at first progression and front-line therapy type was also analyzed. Patients were divided into four subgroups according to use of rituximab up front or not and to HDC-ASCT or none.

For rituximab-naïve patients (patients failing CHVP-I), 3-year EFS rates were 72% (95%CI 51-85%) for transplanted patients (n=29) *vs.* 31% (95%CI 19-44%) for those without HDC-ASCT (n=61) (*P*=0.002). Respective 3-year OS rates were 92% (95%CI 72-98%) for patients who underwent HDC-ASCT *vs.* 60% (95%CI 46-72%) for those without HDC-ASCT (*P*=0.005).

For rituximab treated patients (patients failing R-CHVP-I), 3-year EFS rates were 75% (95%CI 41-91%) for transplanted patients (n=13) *vs.* 49% (95%CI 30-65%) for those without HDC-ASCT (n=50) (*P*=0.052). Respectively, 3-year OS rates were 92% (95%CI 57-99%) for transplanted patients *vs.* 65% (95%CI 46-79%) for non-transplanted patients (*P*=0.052) (Figure 3).

According to the period of progression or relapse

Fifty-seven patients experienced progression while on therapy (induction or consolidation phase). Among these

Table 2. Parameters influencing EFS and OS in univariate and multivariate analysis.

	EFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age at progression	1.02	1-1.04	0.033	1.01	1-1.04	0.3	1.04	1.01-1.07	0.0036	1.03	1-1.06	0.075
Sex	1.4	0.92-2.14	0.11	1.5	0.95-2.4	0.08	1.44	0.83-2.5	0.2	–	–	–
First-line CHVP-I *vs.* R-CHVP-I	0.75	0.48-1.17	0.2	0.78	0.47-1.3	0.33	1.09	0.62-1.9	0.77	–	–	–
FLIPI score (reference=0-1)												
vs. 2	0.46	0.27-0.8	0.013	0.38	0.17-0.85	0.0517	0.49	0.24-1	0.0045	1.48	0.31-7.12	0.214
vs. 3-5	1.9	1.2-3		0.63	0.31-1.3		3.09	1.58-6.05		2.5	0.58-10.8	
Progression/relapse period												
Induction *vs.* follow up	1.64	1.03-2.63	0.001	2.5	1.4-4.38	0.004	1.98	1.1-3.56	0.0004	4.08	1.97-8.4	0.0001
Consolidation *vs.* follow up	1.9	1.14-3.13		2.76	1.55-4.9		2.25	1.22-4.14		3.83	1.83-8	
Chemotherapy type at first relapse												
Fludarabine-based *vs.* other	1.17	0.68-2	0.58	–	–	–	1.63	0.85-3.11	0.14	–	–	–
Anthracycline-based *vs.* other	1	0.6-1.63	0.95	–	–	–	1.54	0.84-2.82	0.16	–	–	–
Cytarabine-based *vs.* other	0.93	0.57-1.52	0.78	–	–	–	1.38	0.76-2.5	0.29	–	–	–
Cyclophosphamide-based *vs.* other	1	0.61-1.63	0.98	–	–	–	1.04	0.56-1.96	0.9	–	–	–
Rituximab at progression (Yes *vs.* No)	0.66	0.42-1.05	0.077	0.65	0.4-1.08	0.095	0.99	0.54-1.8	0.96	–	–	–
Transplantation at progression (Yes *vs.* No)	0.41	0.24-0.71	0.0015	0.38	0.2-0.72	0.003	0.22	0.09-0.56	0.0014	0.26	0.1-0.68	0.006

Only variables associated with a P value of 0.2 in univariate analysis were tested in multivariate analysis. FLIPI: Follicular Lymphoma International Prognostic Index; EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

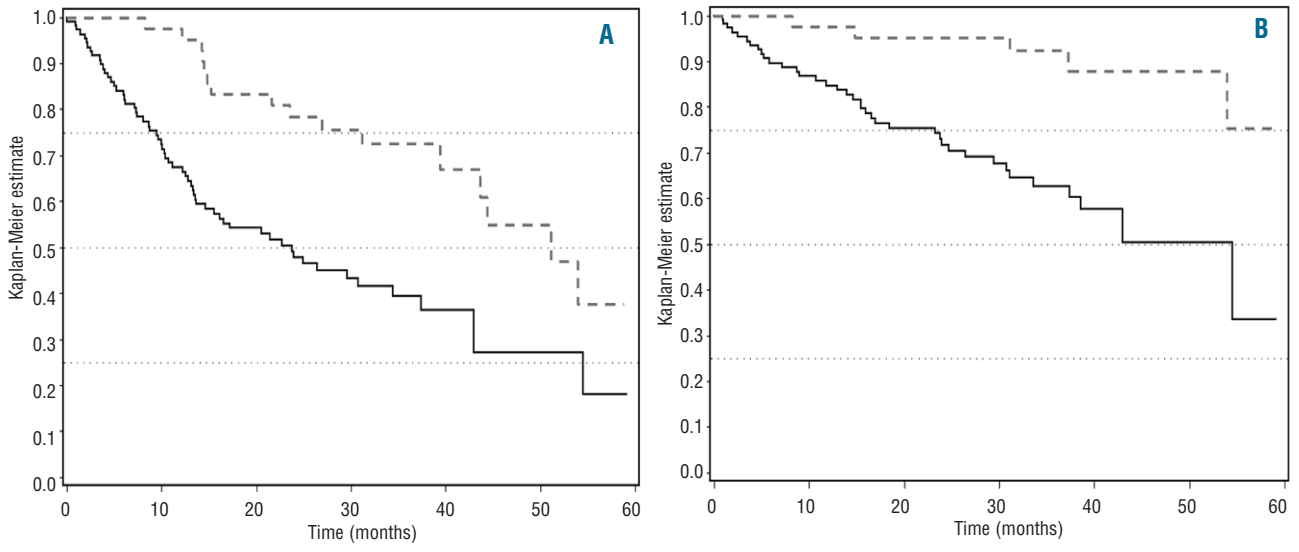

Figure 2. Outcome of patients (under the age of 70 years) according to transplantation at first progression: ----transplanted patients (n=42); —— non-transplanted patients (n=111). (A) Event-free survival (*P*=0.0005). (B) Overall survival (*P*=0.0003).

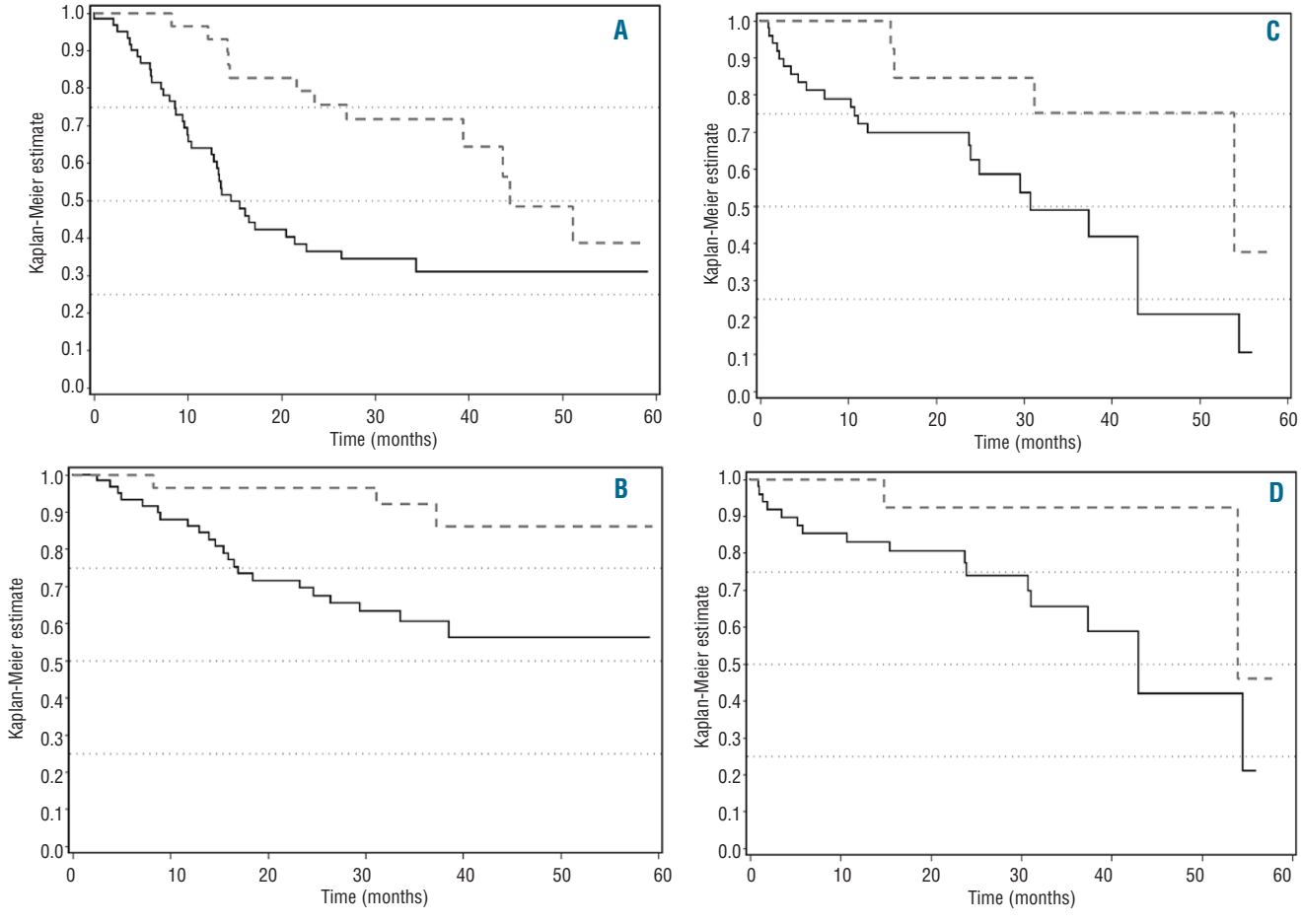

Figure 3. Outcome of patients (under the age of 70 years) according to front-line therapy and use of transplantation at first progression: ---- transplanted patients and —— non-transplanted patients. (A) Event-free survival of patients failing CHVP-I (*P*=0.002). (B) Overall survival of patients failing CHVP-I (*P*=0.005). (C) Event-free survival of patients failing R-CHVP-I (*P*=0.052). (D) Overall survival of patients failing R-CHVP-I (*P*=0.052).

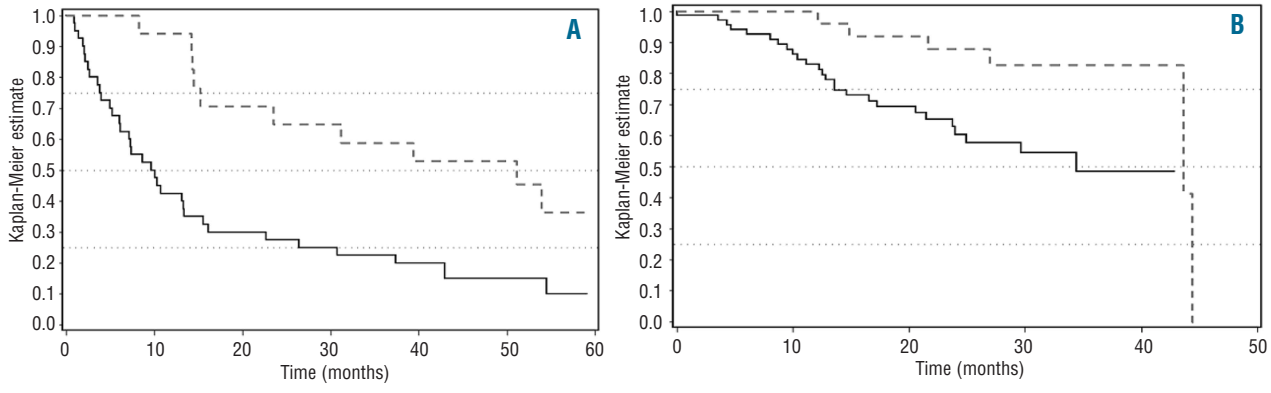

Figure 4. Outcome of patients (under the age of 70 years) according to progression period and use of transplantation at first progression: ---- transplanted patients and —— non-transplanted patients. (A) Event-free survival of primary refractory patients (*P*=0.002). (B) Event-free survival of patients who progressed or relapsed after first-line treatment completion: (*P*=0.011).

patients, 17 underwent HDC-ASCT. The 3-year EFS rate of transplanted patients was 88% (95%CI 61-97%) compared to 40% (95%CI 25-55%) for non-transplanted patients (*P*=0.0002). In this setting, the 3-year OS was also better for transplanted patients: 59% (95%CI 33-78%) *vs.* 23% (95%CI 11-36%) (*P*=0.002). For patients experiencing progression after completing first-line treatment (n=96), the 3-year EFS rate of transplanted patients (n=25) was 83% (95%CI 60-93%) compared to 48% (95%CI 31-64%) for the other (n=71) (*P*=0.01). Three year OS rates were 96% (95%CI 75-88%) for the transplanted group *vs.* 78% for the non-transplanted (95%CI 62-88%) (*P*=0.22) (Figure 4).

Discussion

This study examined the outcome of all relapsed and refractory FL patients enrolled in the FL2000 study. There were no recommendations concerning salvage therapy at first relapse. This analysis thus reflects the impact of investigator choice in everyday practice and of the various strategies applied for FL outside of clinical trials.

Twenty-four percent of patients progressing after first-line treatment underwent HDC-ASCT. As expected, transplanted patients were significantly younger than non-transplanted patients but transplanted patients had experienced earlier relapse after front-line treatment than non-transplanted patients. Our analysis underlines the favorable impact of HDC-ASCT in disease control, with a longer EFS and OS for transplanted *versus* non-transplanted patients. However, since this was a retrospective study, we cannot exclude the possibility that the favorable impact of HDC-ASCT may have been reinforced by selection of patients responding after salvage therapy for transplantation. Indeed, some conditions or reasons precluding transplantation (ineligibility for transplantation due to underlying medical condition, disease refractoriness, local physician or patient decision) could not be accurately assessed in our study. In spite of these potential biases and the retrospective nature of the present analysis, our results indicate that FL patients who present at diagnosis with a high tumor burden as defined in the FL2000 trial, and who experience their first progression after up front treatment, could be good candidates for the option of HDC-ASCT.

Table 3. Detailed characteristics of the 153 patients aged 70 years or under according to the use of HDC-ASCT.

HDG-ASCT at first relapse for patients < or = 70 years	No	Yes	*P* value
Number	111	42	
Male/Female	49/62	25/17	0.09
Median age	60 (25-36)	49.5 (27-68)	0.0002
FLIPI score at diagnosis (missing = 5)			0.004
0-1	11 (10.5%)	13 (31%)	
2	32 (30%)	14 (33%)	
3-5	63 (59.5%)	15 (36%)	
Relapse period			0.7
Induction phase	22 (20%)	11 (26%)	
Consolidation phase	18 (16%)	6 (14%)	
Follow-up period	71 (64%)	25 (60%)	
Chemotherapy regimens at first relapse			
Fludarabine-based	20 (18%)	5 (12%)	0.36
Anthracycline-based	27 (24%)	9 (21.5%)	0.7
Cytarabine-based	20 (18%)	19 (45%)	0.006
Cyclophosphamide-based	24 (22%)	12 (29%)	0.36
Immunotherapy at first relapse			
Yes	73 (66%)	37 (88%)	0.006
Containing rituximab	66 (63%)	34 (81%)	0.006
Time from diagnosis to relapse during follow up	2.95 y (1.9–5.65)	2.45 y (1.6-3.6)	0.02

FLIPI: Follicular Lymphoma International Prognostic Index; HDC-ASCT: high-dose chemotherapy followed by autologous stem cell transplantation.

The present work seems to suggest that transplanted relapsed FL patients have a longer control of disease than non-transplanted. These results are consistent with those recently reported for patients in the GELF-86 and GELF-94 studies.[13] Our study provides additional information on HDC-ASCT in a therapy-failure setting after a first-line rituximab-containing regimen. Subgroup analysis with a limited number of patients suggests that transplantation improves control of disease and survival in patients who fail CHVP-I, regardless of prior rituximab exposure. Nowadays, the use of rituximab in the up front therapy of follicular lymphoma has become a standard of care; thus, the question of the best therapeutic option for rituximab pre-treated patients is of major interest. The present analy-

sis for this subgroup of patients shows that there is a trend for both EFS and OS in favor of the use of HDC-ASCT at first relapse (P=0.052). These encouraging data are also found independently of the timing of disease progression. However, the question of the prolonged impact of HDC-ASCT for rituximab pre-treated FL patients remains open and only a prospective clinical trial can confirm whether or not HDC-ASCT is superior to a conventional approach.

Only one small, and likely underpowered, randomized study suggested a positive survival impact for HD-ASCT in relapsing FL.[14] Besides this, four prospective multicenter randomized trials compared chemotherapy alone with chemotherapy followed by HDC-ASCT as first-line therapy.[11,15-17] These studies, including one performed in the rituximab era, indicated that HDC-ASCT was associated with a better control of disease, but did not improve OS. The recently published 10-year update of the GOELAMS 064 trial showed a plateau phase on the progression-free survival curve for transplanted patients which might suggest that HDC-ASCT could potentially cure some FL patients.[18] The reason for the absence of proven OS benefit is still unclear and may be related to the use of HDC-ASCT as salvage therapy for those patients who did not receive transplantation up front, or to long-term toxicities, including secondary malignancies occurring after HDC-ASCT. However, secondary malignancies have also been reported in non-transplanted patients. Altogether, these previous reports and the present study indicate that HDC-ASCT should be considered as an option in the management of relapsed FL and may in particular improve the outcome for patients with a poor prognosis.

No significant difference was observed in patient outcome according to use of rituximab at first progression. The combination of rituximab and chemotherapy up front has been investigated in four randomized phase III trials. The conclusions of all four trials were in favor of the rituximab-containing regimen and established that rituximab up front improves duration of response.[3-6] Two randomized studies demonstrated that adding rituximab to salvage therapy at first relapse (followed by rituximab maintenance) increased response rates and improved disease-free survival.[19,20] There may be several reasons to explain this discrepancy between the present analysis and previous reports investigating rituximab administration at first relapse. First, the limited number of patients in our study, in particular in the subgroups, may preclude the identification of a statistically significant difference. Second, 40% of the patients in the present study were not rituximab naïve (including 13 patients who progressed during a treatment containing rituximab) while other studies only included rituximab-naïve patients. Indeed, we observed a 3-year EFS rate trend in favor of therapy containing rituximab at first relapse in the rituximab-naïve subgroup. Third, only data regarding second-line treatment were collected and we cannot exclude the use of rituximab for subsequent progressions. That is why the role of rituximab in the common setting of FL relapsing after prior rituximab exposure needs to be confirmed, in particular for patients proceeding to HDC-ASCT.

These results support the role of HDC-ASCT as consolidation therapy at first relapse/progression for FL patients presenting with high tumor burden at diagnosis, independently of any rituximab used up front and of the timing of progression. We recommend systematically considering HDC-ASCT as an option for this patient group. Given the substantial benefits shown when rituximab is maintained in relapsing FL,[20] we suggest that both therapies be incorporated in future trials aimed at improving the outcome for patients with relapsed follicular lymphoma.

Authorship and Disclosures

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