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Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group

Vindi Jurinovic [1,2], Bernd Metzner [3], Michael Pfreundschuh [4], Norbert Schmitz [5], Hannes Wandt [6], Ulrich Keller [7], Peter Dreger [8], Martin Dreyling [1], Wolfgang Hiddemann [1,9,10], Michael Unterhalt [1], Eva Hoster [1,2], Oliver Weigert [1,9,10,*]

[1] *Department of Internal Medicine III, University Hospital of the Ludwig-Maximilians-University, Munich, Germany*
[2] *Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany*
[3] *Department of Hematology/Oncology, University Hospital Oldenburg, Oldenburg, Germany*
[4] *Department of Internal Medicine I, Saarland University Medical School, Homburg, Germany*
[5] *Department of Medicine, Hematology, Oncology, Hemostaseology and Pneumonology, University Hospital of Muenster, Muenster, Germany*
[6] *Department of Hematology and Medical Oncology, Paracelsus Medical University, Nuremberg, Germany*
[7] *Department of Medicine III, Hematology and Medical Oncology, University Hospital of the Technical University of Munich, Munich, Germany*
[8] *Department of Medicine V, University of Heidelberg, Heidelberg, Germany*
[9] *German Cancer Consortium (DKTK), Heidelberg, Germany*
[10] *German Cancer Research Centre (DKFZ), Heidelberg, Germany*

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A B S T R A C T

Patients with follicular lymphoma (FL) and progression of disease (POD) within 24 months after frontline treatment (POD24) have poor overall survival (OS). The optimal salvage treatment for these patients is unknown. We assessed the role of high-dose therapy and autologous stem cell transplantation (ASCT) in transplant-eligible patients. We analyzed 162 patients with advanced-stage FL who had received frontline treatment within the GLSG1996 or GLSG2000 trials. All patients had POD at age ≤ 65 years and had not received a prior transplant. Second-line treatment was not specified by study protocols. Survival was calculated from time of second-line treatment. Eighteen patients (11%) progressed (n = 16) or died (n = 2) during cytoreductive second-line treatment (considered "cytoreduction failure"); none received ASCT, and their median second-line OS was <1 year. A total of 113 patients had POD24 (70%), whereas 49 had POD after 24 months (30%). Sixty-three patients without cytoreduction failure received ASCT (39%), and 81 received no transplant (50%). In patients with POD24, a significant survival benefit was associated with ASCT with a 5-year second-line progression-free survival for ASCT versus no transplant of 51% versus 19% (hazard ratio, .38; 95% confidence interval, .24 to .62; $P < .0001$) and a 5-year second-line OS of 77% versus 59% (hazard ratio, .54, 95% confidence interval, .30 to .95; $P = .031$). Thus, ASCT is an effective treatment option for transplant-eligible patients with high-risk FL as identified by POD24 and should be evaluated in prospective clinical trials.

INTRODUCTION

Follicular lymphoma (FL) is among the most common subtypes of non-Hodgkin lymphoma worldwide, accounting for 20% to 35% of non-Hodgkin lymphoma in the United States and Europe [1,2]. Most patients are diagnosed with advanced-stage disease and cannot be cured with standard immunochemotherapy [3]. Although considered the prototype of non-Hodgkin lymphoma with an indolent clinical course, approximately 20% of patients receiving

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* Correspondence and reprint requests: Oliver Weigert, MD, University Hospital of the Ludwig-Maximilians-University Munich, Medical Department III, Laboratory for Experimental Leukemia- and Lymphoma Research (ELLF), Max-Lebsche Platz 30, 81377 Munich, Germany.
E-mail address: oliver.weigert@med.uni-muenchen.de (O. Weigert).

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immunochemotherapy experience progression of disease within 24 months of frontline treatment (POD24) and have a median overall survival (OS) of <5 years [4,5]. The optimal second-line treatment for these high-risk patients is unclear.

High-dose therapy and autologous stem cell transplantation (ASCT) has been suggested as an effective treatment strategy for patients with POD24 [6,7], primarily because retrospective analyses showed best outcomes when ASCT was applied in earlier lines of treatment for relapsed FL [8-11] and in patients with shorter response duration [12]. However, available data also indicate better outcomes with ASCT in patients with chemotherapy-sensitive disease before transplant [9,10,13-15], so enrichment for chemoresistant tumors in patients with POD24 may limit its activity [6]. A European Society for Blood and Marrow Transplantation consensus document suggested ASCT as an appropriate treatment option for patients with first chemosensitive relapse, especially for patients with short response duration [16], but POD24 has not yet been assessed systematically as a factor associated with efficacy of ASCT. Therefore, we aimed to assess the role of ASCT in transplant-eligible patients with respect to POD24.

METHODS

Patient Selection

Patients from 2 successive randomized trials of the German Low-Grade Lymphoma Study Group (GLSG) for advanced-stage symptomatic FL, GLSG1996 and GLSG2000, were eligible for retrospective analysis of second-line therapy if they had documented first progressive, relapsed, or refractory disease (POD) in need of treatment according to GLSG criteria [17] at age ≤ 65 years. All patients had been eligible but had not been randomized for and had not received consolidative ASCT as part of their frontline treatment (Figure 1). Both trials had been approved by the institutional review board and were carried out in accordance with the Declaration of Helsinki. Patients provided written informed consent. Details on GLSG1996 and GLSG2000 have been published elsewhere [17,18] and are summarized in the Supplementary Data. The choice of second-line treatment at POD was left to the treating physician. However, for patients not assigned to frontline ASCT, ASCT was recommended as second-line treatment by the study protocol. Patient data were obtained from specific questionnaires and from available follow-up documentation. Patients were excluded if no questionnaires were returned.

Definitions and Statistical Methods

POD was defined as progressive, relapsed, or primary refractory disease after systemic frontline treatment. Primary refractory disease was defined as less than a partial response after systemic frontline treatment. POD24 was POD within 24 months after initiation of systemic frontline treatment for

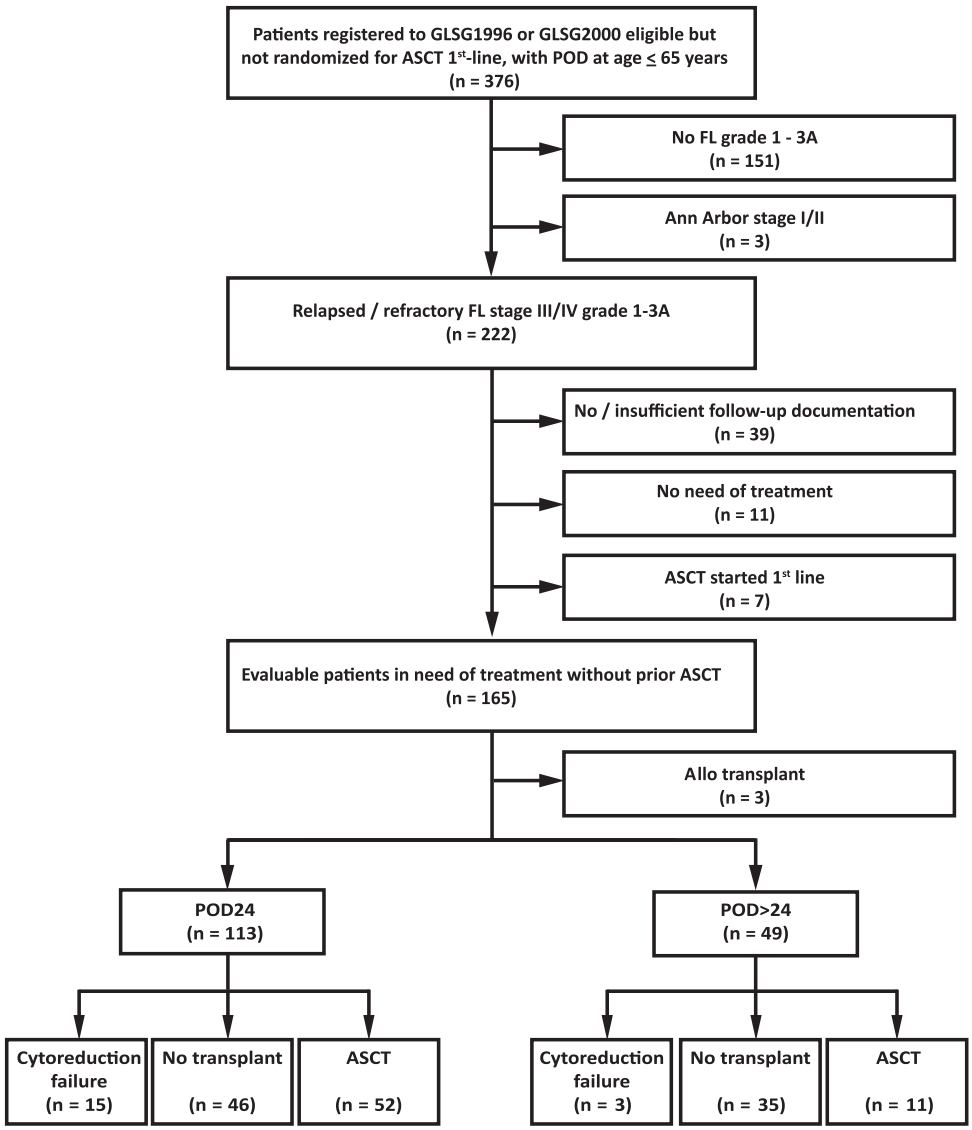

Figure 1. CONSORT diagram for patient selection. Allo transplant indicates allogeneic hematopoietic stem cell transplantation.

symptomatic FL, whereas POD > 24 refers to POD after 24 months. Cytoreduction failure was defined as progressive disease or death in response to cytoreductive second-line treatment. When indicated, hazard ratios (HRs) and *P*-values for treatment effects were adjusted for dichotomized Follicular Lymphoma International Prognostic Index (FLIPI; high risk versus non–high risk) and time-to-POD (as a continuous variable). For intention-to-treat (ITT) analyses, patients without cytoreduction failure were considered as ASCT if there had been an attempt to collect an autograft as documented by initiation of a treatment regimen to mobilize hematopoietic stem cells, irrespective of whether or not ASCT was completed.

The primary endpoints of this analysis were second-line progression-free survival (PFS), calculated from time of initiation of second-line treatment to progression, relapse, or death from any cause, and second-line OS, calculated from time of initiation of second-line treatment to date of death, respectively. All statistical analyses were carried out with the statistical software R (version 3.3.1; R Core Team, Vienna, Austria). The R-package *survival* (2.39-4) was used for survival analyses. The log-rank test was used for univariate analyses and the Cox proportional hazards regression for multivariate analyses. Categorical variables were compared with the χ^2 test. Numerical variables were analyzed with the Mann-Whitney U test or, when more than 2 groups were compared, the Kruskal-Wallis test.

RESULTS

A total of 165 patients from the GLSG1996 and GLSG2000 trials met the eligibility criteria for this study. Three patients received allogeneic transplants as second-line treatment (2%) and were excluded from further analyses. Of the remaining 162 patients, 113 patients (70%) had POD24. Forty-nine patients (30%) experienced POD > 24 (Figure 1). Patient characteristics are noted in Supplementary Table S1.

POD24 Cohort

Median time to POD was 10.7 months (95% confidence interval [CI], 9.8 to 12.4) for POD24 patients and 41.5 months (95% CI, 37.1 to 48.0) for POD > 24. Age, gender, and frontline treatment regimens were not significantly different in patients with POD24 and POD > 24. At the time of treatment initiation, patients who subsequently experienced POD24 more often had elevated serum lactate dehydrogenase levels (34% versus 14%, $P = .0196$) and high-risk FLIPI (43% versus 10%, $P = .011$), whereas the other clinical risk factors of the FLIPI were not significantly different (Supplementary Table S1).

Patients with POD24 more often received dose-intensified cytoreductive second-line regimens (50% versus 22% for POD24, $P = .0017$), whereas rituximab was more commonly added to second-line regimens in patients with POD > 24 (25% versus 48%, $P = .018$). Among the 148 patients assessable for treatment response after cytoreductive second-line therapy, patients with POD24 had a lower complete response rate (25% versus 48%, $P = .017$), but the overall response rate was not significantly different (79% versus 83%, $P = .82$).

With a median follow-up of 11.2 years, POD24 patients had a significantly shorter survival compared with patients with POD > 24 (5-year second-line OS rates, 60% versus 83%: HR, 1.93: 95% CI, 1.10 to 3.40; $P = .02$). The 5-year second-line PFS rates were 31% versus 49% (HR, 1.43; 95% CI, .95 to 2.14; $P = .086$), respectively (Supplementary Figure S1).

ASCT Cohort

A total of 63 patients received ASCT (39%): 52 had POD24, and 11 had POD > 24. Ninety-nine patients did not receive a transplant as second-line treatment (61%), in which 61 had POD24 and 38 had POD > 24 (Figure 1). The median time between POD and ASCT was 4.8 months (range, 1 to 13).

ASCT was more commonly applied in men (68% versus 51%) and younger patients (median age 47 versus 51 years at time of frontline treatment and 48 versus 53 years at second-line treatment, respectively). Frontline treatment regimens were not different in patients who received ASCT versus no transplant, and only 20 patients (12%) had received a rituximab-containing frontline regimen (Supplementary Table S2). No patient received rituximab maintenance after ASCT.

Time to POD was shorter for patients who received ASCT compared with patients who received no transplant (1.1 years versus 1.5 years, $P = .0033$). Patients who received ASCT less often had elevated serum lactate dehydrogenase levels at the time of POD (12% versus 36%), whereas the other clinical risk factors of the FLIPI were not different (Supplementary Table S2).

Cytoreductive Second-Line Treatment

An overview of cytoreductive second-line treatments is provided in Supplementary Table S3. Patients who received ASCT more commonly received dose-intensified cytoreductive second-line regimens (78% versus 19%; Supplementary Tables S2 and S4). In 148 patients with assessable response assessment after cytoreductive second-line treatment, overall response rate was higher in patients who subsequently received ASCT (92% versus 74%; Supplementary Table S2). Sixteen patients had progressive disease and did not qualify for subsequent ASCT, and another 2 patients died after cytoreductive second-line treatment; these patients were considered cytoreduction failures and their outcomes were analyzed separately. Rituximab was added to second-line regimens in 54% and 55% of patients who received ASCT or no transplant, respectively (Supplementary Tables S3 and S4). The rate of cytoreduction failures was lower in patients who received second-line rituximab (5% [4/88] versus 19% [14/74]).

Patients with cytoreduction failure had dismal treatment outcomes (Figure 2C,D), with a median survival of only 8.4 months. This cohort was enriched for patients with primary refractory FL (33% [6/18] versus 14% [20/144]) and shorter time to POD: 15 of 18 patients with cytoreduction failure had POD24, and their median time to POD was only 10.2 months (95% CI, 4.5 to 21.5).

Outcome of Patients Who Received ASCT

An overview of mobilization and high-dose regimens is provided in Supplementary Table S5: 51% of patients (32/63) received the BEAM protocol (carmustine, etoposide, cytarabine, and melphalan), and 27% (17/63) received total body irradiation–based regimens. Supplementary Table S6 summarizes the major toxicity associated with ASCT. One patient died within 3 months after ASCT (2%) from staphylococcal sepsis.

In patients who received ASCT, the complete response rate increased from 25% (13/52 patients with assessable assessment of treatment response before ASCT) to 70% (43/61 patients with assessment of treatment response after ASCT) and the overall response rate from 92% (48/52) to 98% (60/61) (Supplementary Table S7). Patients who received ASCT had significantly higher 5-year second-line PFS rates (52% versus 27%; HR, .47; 95% CI, .31 to .70; $P = .00012$) and 5-year second-line OS rates (78% versus 60%; HR, .53; 95% CI, .32 to .86; $P = .0086$; Figure 2A,B).

However, responsiveness to salvage therapy affects the decision to proceed to ASCT and introduces a relevant selection bias. When restricting the analysis to patients without cytoreduction failure, the differences in 5-year second-line PFS decreased to 52% versus 33% (HR, .56; 95% CI, .37 to .84;

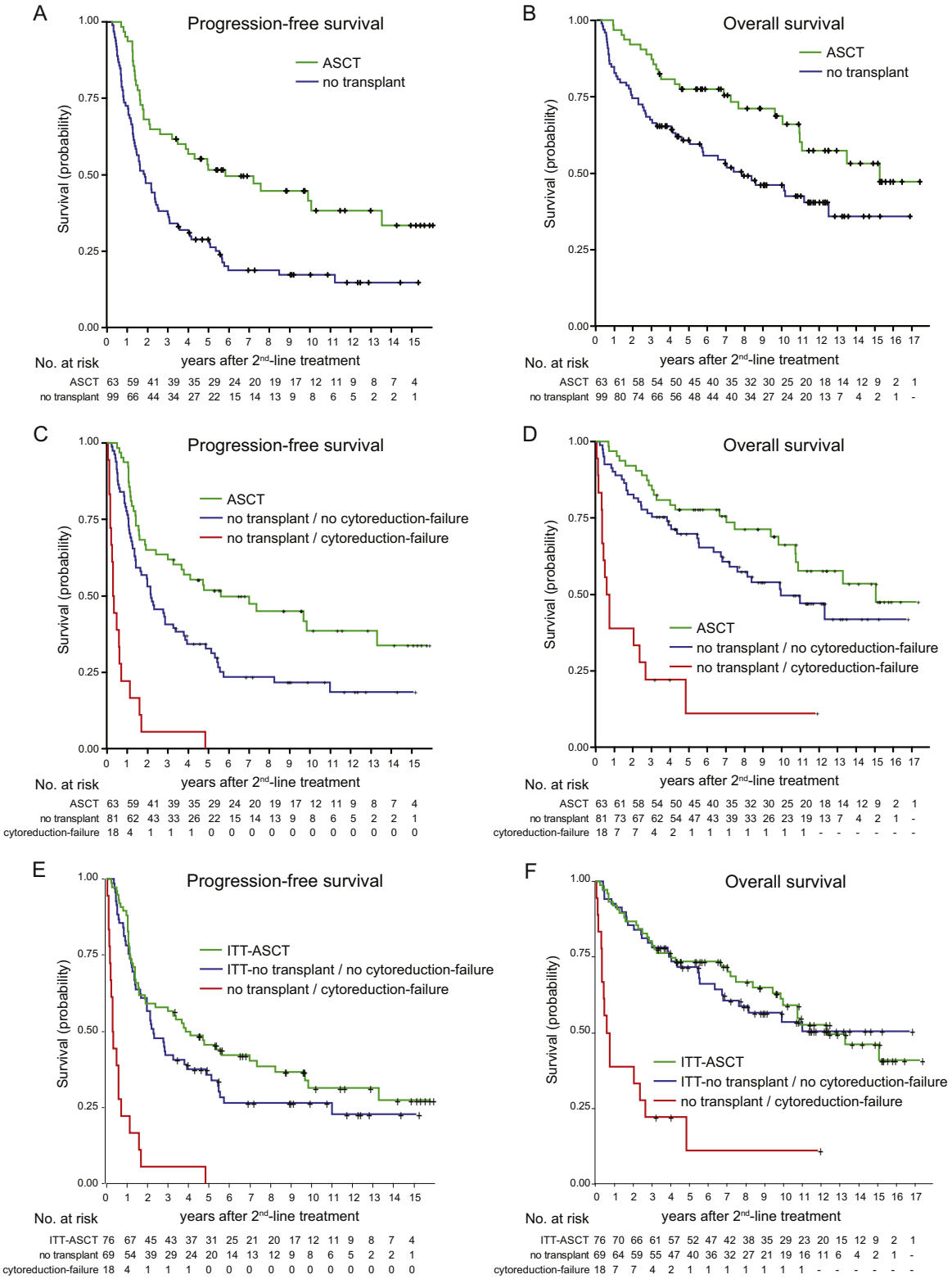

Figure 2. Treatment outcome for ASCT or no transplant in patients with POD. Second-line PFS (A) and second-line OS (B) for patients with POD who received ASCT or no transplant. ASCT versus no transplant for second-line PFS: HR, .47; 95% CI, .31 to .70; $P = .00012$; adjusted HR, .33; 95% CI, .22 to .50; $P < .0001$. ASCT versus no transplant for second-line OS: HR, .53; 95% CI, .32 to .86; $P = .0086$; adjusted HR, .39; 95% CI, .23 to .64; $P = .00022$. Second-line PFS (C) and second-line OS (D) for patients with POD who received ASCT or no transplant (with or without prior cytoreduction failure). ASCT versus no transplant/no cytoreduction failure for second-line PFS: HR, .56; 95% CI, .37 to .84; $P = .0048$; adjusted HR, .42; 95% CI, .27 to .65; $P = .0001$. ASCT versus no transplant/no cytoreduction failure for second-line OS: HR, .76; 95% CI, .40 to 1.12; $P = .12$; adjusted HR, .55; 95% CI, .32 to .93; $P = .025$. Second-line PFS (E) and second-line OS (F) for all patients with POD who received ASCT by ITT (ITT-ASCT) or no transplant (with or without prior cytoreduction failure). ITT-ASCT versus ITT-no transplant/no cytoreduction failure for second-line PFS: HR, .77; 95% CI, .52 to 1.14; $P = .19$; adjusted HR, .57; 95% CI, .37 to .89; $P = .012$. ITT-ASCT versus ITT-no transplant/no cytoreduction failure for second-line OS: HR, .93; 95% CI, .47 to 1.53; $P = .78$; adjusted HR, .72; 95% CI, .43;1.23; $P = .23$. Patients with cytoreduction failures (n = 18, all no transplant) were analyzed separately. Patients who received allo transplant (n = 3) were excluded from analysis.

$P = .0048$), and the 5-year second-line OS rates were no longer significantly different (78% versus 70%; HR, .76; 95% CI, .40 to 1.12; $P = .12$; Figure 2C,D) between transplant-eligible patients who actually received ASCT and those who did not.

Outcome of Patients Intended to Receive ASCT

Still, a subset of patients in the no-transplant group would have been intended to receive ASCT. In fact, 15 patients received a stem cell mobilizing regimen but did not proceed with ASCT, including 1 patient who ultimately received an allogeneic transplant as second-line treatment. The most common reasons not to proceed with ASCT were mobilization failures (7/15, 47%) and toxicity (5/15, 33%; Supplementary Table S8). Even though mobilized patients with cytoreduction failure were analyzed separately, failure to complete ASCT was associated with significantly inferior 5-year second-line PFS compared with patients who received ASCT (17% versus 52%; HR, 3.57; 95% CI, 1.85 to 7.14; $P < .0001$) and second-line OS (58% versus 78%; HR, 2.63; 95% CI, 1.19 to 5.56; $P = .012$; Supplementary Figure S2).

When comparing chemosensitive patients who received a stem cell mobilizing regimen by ITT, irrespective of whether or not they completed ASCT, with patients who had not received mobilization treatment, the differences in 5-year second-line PFS for ITT with or without ASCT versus ITT with no transplant further decreased to 46% versus 36% (HR, .77; 95% CI, .52 to 1.14; $P = .19$), and OS curves were essentially superimposable (5-year second-line OS, 74% versus 72%; HR, .93; 95% CI, .47 to 1.53; $P = .78$; Figure 2E,F). These analyses question the utility of ASCT in unselected cohorts of patients with first POD.

ASCT for Patients Stratified by POD24

Fifty-two patients with POD24 received ASCT (46%) as compared with 11 with POD > 24 (22%, $P = .008$). The clinical characteristics of patients who received ASCT or no transplant according to POD24 status are noted in Table 1.

For patients who did not receive a transplant, POD24 was predictive for inferior 5-year second-line PFS (14% versus 47%; HR, 2.43; 95% CI, 1.51 to 3.93; $P = .00018$) and 5-year second-line OS (45% versus 83%; HR, 2.72; 95% CI, 1.43 to 5.19; $P = .0015$; Figure 3A,B). Patients with POD24, however, who received ASCT had significantly improved 5-year second-line PFS (51% versus 19%; HR, .38; 95% CI, .24 to .62; $P < .0001$) and 5-year second-line OS (77% versus 59%; HR, .54; 95% CI, .30 to .95; $P = .031$) compared with patients who received no transplant (Figure 3A,B). In fact, patients with POD24 who received ASCT had comparable outcomes with patients with POD > 24 (Figure 3A,B). When patient outcomes were analyzed by ITT, the 5-year second-line PFS was still 46% versus 18% (HR, .53; 95% CI, .33 to .86; $P = .0086$) and 5-year second-line OS 73% versus 58% (HR, .76; 95% CI, .76 to 1.35; $P = .35$; Figure 3C,D).

Next, we analyzed only the subgroup of patients with POD24 who received rituximab as part of their second-line treatment, that is, the current standard of care [1-3,19,20]. This included 48% of patients who received ASCT (25/52) and 48% of patients who received no transplant (29/51). Most assessable patients (42/54, 78%) had not received frontline rituximab. In POD24 patients without cytoreduction failure, receiving an ASCT was associated with a significantly higher 5-year second-line PFS compared with not receiving a transplant (60% versus 18%; HR, .39; 95% CI, .19 to .79; $P = .0068$).

Table 1
Clinical Characteristics of Patients Who Received ASCT or No Transplant as Second-Line Treatment* According to POD24 Status

Characteristics		No. Assessable Patients	POD24		POD > 24		*P*
			ASCT (n = 52)	No Transplant (n = 61)	ASCT (n = 11)	No Transplant (n = 38)	
First-line treatment							
Median age, yr (range)		162	47 (21-60)	51 (19-60)	47 (35-60)	51 (33-60)	.14
Male gender		162	38 (73)	31 (51)	5 (83)	19 (50)	.050
Clinical risk factors	High-risk FLIPI	162	20 (39)	28 (46)	3 (27)	7 (25)	.041
	Nodal sites > 4	162	41 (79)	48 (79)	9 (82)	27 (71)	.78
	LDH elevated	162	14 (27)	24 (39)	2 (18)	5 (13)	.034
	Hb < 120 g/L	162	12 (23)	19 (31)	2 (18)	8 (21)	.59
	ECOG > 1	162	5 (10)	13 (21)	0 (0)	5 (13)	.15
Treatment	CHOP	162	37 (71)	44 (72)	10 (91)	28 (74)	.32
	MCP		5 (10)	12 (20)	1 (9)	5 (13)	
	R-CHOP		10 (19)	5 (8)	0 (0)	5 (13)	
Second-line treatment							
Median age, yr (range)		162	48 [22-60]	52 [19-62]	53 (39-63)	55 (36-65)	.028
Age > 60 yr		162	1 (2)	6 (10)	1 (9)	7 (18)	.067
Clinical risk factors	Nodal sites > 4	130	16 (37)	15 (31)	3 (30)	6 (21)	.57
	LDH elevated	101	5 (14)	15 (41)	0 (0)	4 (19)	.018
	Hb < 120 g/L	117	7 (18)	18 (41)	4 (57)	5 (19)	.024
	ECOG > 1	102	3 (7)	4 (11)	0 (0)	0 (0)	.41
Treatment	R-containing regimen	162	25 (48)	29 (48)	9 (82)	25 (66)	.063
	Dose-intensified regimens	162	40 (77)	17 (28)	9 (82)	2 (5)	<.0001
Best response to cytoreductive second-line treatment/before ASCT	CR	148	11 (26)	14 (24)	2 (22)	20 (54)	.00048
	Partial response		30 (70)	26 (44)	5 (56)	11 (30)	
	SD		2 (5)	4 (7)	2 (22)	3 (8)	
	Progressive disease		0 (0)	14 (24)	0 (0)	2 (5)	
	Death		0 (0)	1 (2)	0 (0)	1 (3)	
	CR + partial response		41 (95)	40 (68)	7 (78)	31 (84)	.0063

Values are n (%) unless otherwise defined. LDH indicates serum lactate dehydrogenase; Hb, hemoglobin; ECOG, Eastern Cooperative Oncology Group Performance Status; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; MCP, mitoxantrone, chlorambucil, prednisone; R, rituximab; CR, complete response; SD, stable disease.

* Patients receiving ASCT as second-line treatment were excluded from this analysis.

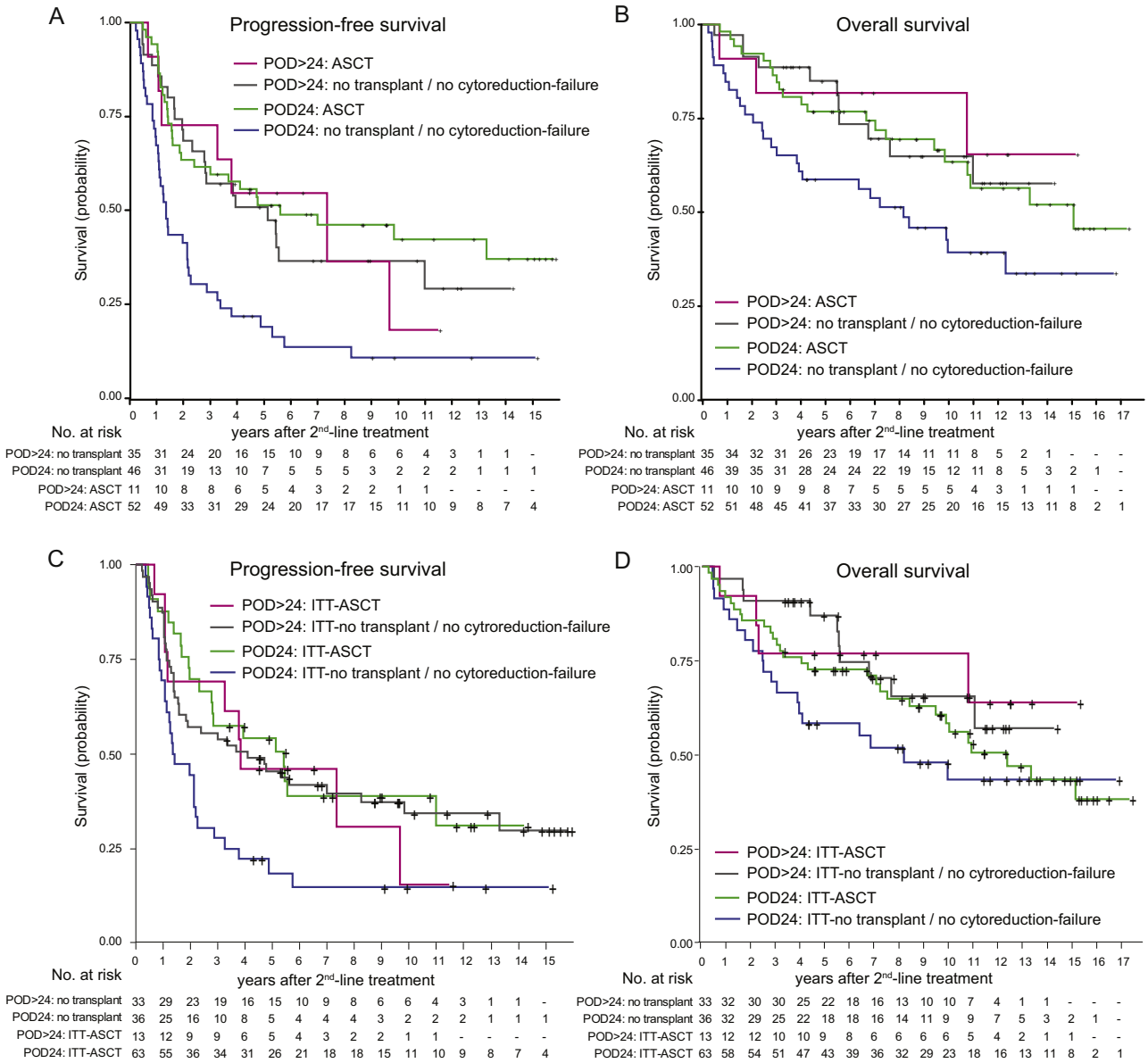

Figure 3. Treatment outcome for ASCT or no transplant according to patients with POD24. Second-line PFS (A) and second-line OS (B) for patients according to POD24 status who received ASCT or no transplant (without prior cytoreduction failure). ASCT versus no transplant/no cytoreduction failure for second-line PFS in POD24: HR, .38; 95% CI, .24 to .62; $P < .0001$; adjusted HR, .36; 95% CI, .22 to .59; $P < .0001$. ASCT versus no transplant/no cytoreduction failure for second-line OS in POD24: HR, .54; 95% CI, .30 to .95; $P = .031$; adjusted HR, .52; 95% CI, .29 to .93; $P = .027$. Second-line PFS (C) and second-line OS (D) for patients according to POD24 status who received ASCT by ITT (ITT-ASCT) or no transplant (without prior cytoreduction failure). ITT-ASCT versus ITT-no transplant/no cytoreduction failure for second-line PFS in POD24: HR, .53; 95% CI, .33 to .86; $P = .0086$; adjusted HR, .49; 95% CI, .30 to .80; $P = .0041$. ITT-ASCT versus ITT-no transplant/no cytoreduction failure for second-line OS in POD24: HR, .76; 95% CI, .76 to 1.35; $P = .35$; adjusted HR, .70; 95% CI, .38 to 1.26; $P = .23$. Patients with cytoreduction failures (all no transplant) were excluded from this analysis.

Five-year second-line OS was 72% versus 65% for those receiving ASCT versus those receiving no transplant (HR, .91; 95% CI, .40 to 2.03; $P = .81$) and 33% for patients who failed second-line immunochemotherapy (Supplementary Figure S3).

Finally, we performed multivariable analyses to assess the impact of ASCT and second-line rituximab on treatment outcome in transplant-eligible patients, that is, excluding patients with cytoreduction failures. In addition, we adjusted for FLIPI and time to POD. ASCT had the strongest impact on favorable treatment outcome and was independently and significantly associated with longer second-line PFS and second-line OS for patients with POD24 (Table 2).

DISCUSSION

Early progression of FL after frontline immunochemotherapy is currently the strongest predictor of poor survival [3,21]. Identifying effective treatment strategies for these high-risk patients is a major clinical priority, particularly for younger patients with lower risk of death from non–FL-related causes. We show that ASCT in patients with POD24 significantly improves second-line PFS and second-line OS with treatment outcomes comparable with patients with POD > 24.

The 24-month cut-off was previously established in patients receiving frontline immunochemotherapy and identified

Table 2
Multivariable Analysis of Second-Line Therapeutic Strategies and Treatment Outcome

		Second-Line PFS			Second-Line OS		
		HR	95% CI	*P*	HR	95% CI	*P*
All transplant-eligible patients (n = 144)	ASCT	.39	.25-.62	<.0001	.53	.31-.90	.020
	Second-line rituximab	.71	.48-1.07	.11	.84	.50-1.40	.50
	FLIPI*	1.63	1.07-2.50	.023	1.31	.78-2.20	.31
	Time to POD†	.98	.97-1.00	.017	.98	.96-1.00	.024
Transplant-eligible patients with POD24 (n = 98)	ASCT	.33	.20-.54	<.0001	.50	.27-.90	.022
	Second-line rituximab	.65	.39-1.06	.084	.84	.46-1.51	.55
	FLIPI*	1.59	.97-2.61	.064	1.18	.66-2.12	.57
	Time to POD†	.98	.94-1.03	.47	.97	.92-1.02	.21

* Dichotomized FLIPI at time of first-line treatment.
† Time to POD as continuous variable.

17% to 26% at significantly increased risk of early death [4,5]. However, most patients in the reference cohorts of these studies had not actually experienced POD. In contrast, our current study was highly enriched for high-risk patients: 100% of patients had POD, 70% had POD24, and time to POD for patients with POD > 24 was only 41.5 months. Importantly, POD24 was still associated with significantly shorter PFS and OS calculated from second-line treatment, confirming the clinical utility of the 24-month cut-off also in younger, transplant-eligible patients with POD.

A limitation of our study is its retrospective character and the possibility of patient selection bias. Generally, retrospective analyses overestimate treatment outcomes of patients who receive ASCT because these cohorts are positively selected for successful cytoreduction and mobilization treatment and tolerable toxicity. Yet, treatment outcomes of patients who receive no transplant are underestimated, especially if these cohorts contain patients with cytoreduction failures and other complications that preclude ASCT, including stem cell mobilization failure and serious or fatal toxicity. We carefully addressed these issues by stringently separating out patients with cytoreduction failures and by analyzing ASCT by ITT. These analyses demonstrated a remarkably demagnified clinical benefit from ASCT in unselected cohorts of patients with first POD.

The second limitation of our analysis is the low fraction of patients who received rituximab-containing frontline regimens—the inherent shortcoming of a study with a median follow-up time of 11.4 years, which spanned the change in standard care of FL. Reassuringly, our findings are consistent with a back-to-back analysis by Casulo et al. [22] in patients who received frontline rituximab chemotherapy: Registry data from the Center for International Blood and Marrow Transplant Research and the National LymphoCare Study showed that ASCT was only associated with improved OS if performed early (ie, within 1 year) in patients with POD24.

Rituximab-containing second-line regimens have significantly improved treatment results for relapsed/refractory FL, in particular in rituximab-naive patients [6,7,19,20]. In our analysis, however, ASCT had a greater impact on improved treatment outcome compared with second-line rituximab. Similar results have been reported by Le Gouill et al. for patients with POD from the FL2000 trial [9-12]. In contrast, Sebban et al. [23] reported a stronger impact of rituximab compared with ASCT in patients with POD from the GELF-86 and GELF-94 trials, but these patients had all been rituximab naive and less enriched for early progressors. We observed the highest 5-year second-line PFS rates in patients who received second-line rituximab plus ASCT (61% in the overall cohort, 60% in the POD24 cohort). Somewhat surprisingly, this did not translate into a significant survival benefit for ASCT versus no transplant, but numbers in these subgroups were small, and interpretation of OS data is particularly challenging in younger patients who qualify for several subsequent lines of therapy. Available data do not indicate any excess toxicity for ASCT in combination with rituximab [12,14,23,24].

Currently, it is unclear if ASCT exerts preferential activity in early progressors or whether the nontransplant regimens used in this study were particularly ineffective in these patients. Ultimately, novel treatment strategies that have become available in the meantime will have to be compared with ASCT in transplant-eligible patients with POD24. Furthermore, nonchemotherapy approaches, such as immune checkpoint blockade, chimeric antigen receptor T cells, or allogeneic transplant, should be exploited in patients with chemoresistant tumors, which remain a major unresolved challenge as demonstrated by the dismal outcome of patients with cytoreduction failure.

It will be key to better define the tumor biology in patients with early POD, and particularly chemoresistant disease. For example, early progressing FL has been reported to be enriched for gene mutations that are otherwise rare in FL overall, including *TP53*, and a clonal architecture that is relatively preserved during treatment, suggesting the presence of resistance properties at diagnosis [9,10,13,14,25]. It is an intriguing hypothesis that common progenitor cells [6,26,27] that give rise to early POD may be particularly sensitive to high-dose therapy and ASCT, which might also explain the molecular and long-term remissions observed in a subset of patients [11,16,28,29].

Finally, ASCT might also act by targeting the tumor microenvironment, which is known to contribute to treatment resistance in FL [17,30]. Although conventional chemotherapy can create “chemoresistant niches” that promote the survival of a minimal residual disease and serve as reservoirs for relapse [17,18,31], higher doses of chemotherapy, and cyclophosphamide in particular, have been shown to resensitize a protective tumor microenvironment to antibody-dependent cellular cytotoxicity by eliciting a stress-related cytokine mediated acute secretory activating phenotype: Monocytes and macrophages, the central effectors of antibody-dependent cellular cytotoxicity, are activated and recruited into the tumor microenvironment as shown in various in vivo model systems including rituximab treatment [4,5,32] and, at the same time, expression of macrophage inhibiting molecules, such as CD47, are suppressed on tumor cell surfaces [33].

In summary, our data suggest that ASCT is an effective treatment option for transplant-eligible patients with

high-risk FL as identified by POD24 and should be evaluated in prospective clinical trials. It remains to be determined if ASCT is also an effective frontline treatment strategy for selected patients identified to be high risk by risk classifiers at initial diagnosis, such as the clinicogenetic risk model m7-FLIPI [34], which has been shown to be predictive for POD24 [5].

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.03.022.

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