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REGULAR ARTICLE

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Trends in postrelapse survival in classic Hodgkin lymphoma patients after experiencing therapy failure following auto-HCT

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Key Points

- PR-OS of cHL patients has improved in recent years, likely due to incorporation of novel therapies and more effective use of allo-HCT.
- Future research should focus on earlier integration of novel therapies for patients with refractory disease to improve outcomes further.

Patients with classic Hodgkin lymphoma (cHL) who relapse after autologous hematopoietic cell transplantation (auto-HCT) historically have had poor outcomes. We hypothesized that, post–auto-HCT relapse, overall survival (PR-OS) has improved in recent years as a result of more widespread use of novel therapies and allogeneic HCT (allo-HCT). We conducted a retrospective study in 4 US academic centers, evaluating 215 patients who underwent auto-HCT from 2005 to 2016 and relapsed thereafter. Patients were divided into 2 cohorts based on timing of auto-HCT, 2005 through 2010 (cohort 1; n = 118) and 2011 to 2016 (cohort 2; n = 97), to compare differences in clinical outcomes. The median age and disease status at auto-HCT were similar in cohorts 1 and 2. The proportions of patients who received brentuximab vedotin (Bv; 55% vs 69%; $P = .07$), checkpoint inhibitors (CPIs; 3% vs 36%; $P \leq .001$), and allogeneic-HCT (22% vs 35%, $P = .03$) were significantly different between cohorts 1 and 2, respectively. At the 5-year follow-up after auto relapse, 32% and 50% of patients were alive in cohorts 1 and 2, respectively ($P = .01$). In multivariate analysis for PR-OS, cohort 1 vs 2 (hazard ratio [HR], 2.3; 95% confidence interval [CI], 1.14-4.60; $P = .01$), age at auto-HCT (HR, 1.48; 95% CI, 1.18-1.87; $P \leq .001$), and time to relapse from auto-HCT (HR, 0.59; 95% CI, 0.47-74; $P \leq .0001$), retained independent prognostic significance for PR-OS. Our study supports the hypothesis that survival of cHL patients after auto-HCT failure has significantly improved in recent years, most likely because of incorporation of novel therapies and more widespread use of allo-HCT.

Introduction

Classic Hodgkin lymphoma (cHL) is a highly curable disease; however, 10% of patients with limited-stage disease and 20% to 30% of patients with advanced-stage disease still experience failure of first-line treatment.[1,2] Autologous hematopoietic cell transplantation (auto-HCT) is the standard of care for patients who do not achieve remission with first-line therapy, or who relapse after induction chemotherapy.[3-5] Auto-HCT provides durable remission in 30% to 70% of patients, depending on remission status before transplant. Therefore, ~50% of cHL patients will ultimately relapse after auto-HCT. These patients historically have had poor outcomes, with median survival in the 1.5-year range, without a significant improvement in patients undergoing auto-HCT from 2000 through 2007 vs 1990 through 2000.[6] A small proportion of such cHL patients may eventually undergo allogeneic HCT (allo-HCT) and then achieve long-term remission.[7-9] For the remainder, disease control is the goal. In recent years, there have been important new innovations in cHL treatment, including brentuximab vedotin (Bv) and checkpoint inhibitors (CPIs), such as nivolumab and pembrolizumab.[10-12] These agents have been shown to have high response rates in patients with relapsed refractory cHL. In the case of Bv, a subgroup may in fact be

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Original data are available by e-mail to the corresponding author.

Table 1. Baseline characteristics

Variables	Total (N = 215)	Cohort 1, 2005-2010 (n = 118)	Cohort 2, 2011-2016 (n = 97)	P
Age at diagnosis, median (range), y	32 (19-72)	32 (19-72)	32 (19-68)	.59*
Age at auto-HCT, median (range), y	35 (19-73)	35 (20-73)	34 (19-71)	.77*
Time from diagnosis to transplant, median (range), mo	18 (5-240)	21 (6-159)	16 (5-240)	.03*
Time from transplant to relapse, median (range), mo	6 (1-103)	6 (1-103)	6.5 (1-59)	.57*
Disease status before auto-HCT, n (%)				.002*
CR	72 (34)	28 (24)	44 (45)	
PR	121 (56)	76 (64)	45 (46)	
SD	9 (4)	6 (5)	3 (3)	
PD	13 (6)	8 (7)	5 (5)	
ECOG PS at auto-HCT, n (%)				.005†
0	55 (42)	32 (56)	23 (31.5)	
1-2	75 (58)	25 (44)	50 (68.5)	
Data missing	85	61	24	
PET status before auto-HCT, n (%)				.37†
Negative	81 (41.5)	41 (39)	40 (45)	
Positive	114 (58.5)	65 (61)	49 (55)	
Data missing	20	12	8	
Best response after auto-HCT, n (%)				.75*
CR	114 (53)	60 (51)	54 (56)	
PR	39 (18)	29 (25)	10 (10)	
SD	17 (8)	10 (8.5)	7 (7)	
PD	44 (20.5)	19 (16)	25 (26)	
Unknown	1 (0.5)	0	1 (1)	
Postrelapse lines of therapy, median (range), n	2.0 (0.0-13.0)	2.0 (0.0-13.0)	2.0 (0.0-7.0)	.07*

ECOG PS, Eastern Cooperative Oncology Group performance status.
*Wilcoxon rank-sum test.
†χ^2 test.

cured.[13] In addition to Bv and the PD-1 inhibitors, several other novel agents are being evaluated for cHL and may contribute to improved survival after auto-HCT failure.

We have observed a trend of anecdotally reported improved survival in cHL patients after auto-HCT failure in recent years. This observation led us to hypothesize that patients are living longer after auto-HCT failure, because of the availability of several new and novel therapies. To properly design trials for this group of patients, it will be important to establish modern benchmarks of what the expected survival is today with our current arsenal of available treatments. We therefore conducted a multicenter retrospective study to evaluate survival of cHL patients after the failure of an auto-HCT, comparing 2 different eras.

Methods

We conducted a multicenter retrospective study in 4 academic institutions in the United States (Medical College of Wisconsin, The Ohio State University, MD Anderson Cancer Center, and Washington University in St. Louis) to evaluate survival of cHL patients after the failure of an auto-HCT. For the purpose of analysis, patients were divided into 2 cohorts based on the timing of auto-HCT, 2005 to 2010 (cohort 1) and 2011 to 2016 (cohort 2), to compare differences in treatment strategies and clinical outcomes.

We also sought to find post–auto-HCT-relapse survival and the difference in survival between the 2 cohorts. Time to relapse was defined as the time from auto-HCT to first documented evidence of cHL relapse or progression. The documentation of relapse after auto-HCT or after successive salvage therapies was determined by the investigator at the participating center, supported by radiological and/or histological confirmation. Overall survival (OS) was measured from the date of relapse after auto-HCT to date of death or last follow-up. This study was approved by the institutional review boards of all 4 centers.

Descriptive statistics were used to describe the patient population, overall and as divided into the 2 cohorts. Univariate between-group comparisons were performed using the Student *t* test, Wilcoxon rank-sum test, or χ^2 test, as indicated depending on the variable type. Overall survival was counted from the date of auto-HCT to death and progression free-survival (PFS) was counted from auto-HCT to disease progression or death. Patients alive without the event of interest were censored at the last follow-up. Kaplan-Meier estimates were used to visualize the survival experience of the cohort and compared via the log-rank test. Left truncation was used for analyzing survival from the time of auto-HCT, because the patients did not enter the study cohort until the time of relapse or progression. It was used to account for the variable timing of relapse

Table 2. Therapies after auto-HCT in 2 cohorts

Variables	Total (N = 215), n (%)	Cohort 1, 2005-2010 (n = 118), n (%)	Cohort 2, 2011-2016 (n = 97), n (%)	*P*
Anthracycline based (evaluable n = 133)	31 (23)	17 (28)	14 (19)	.25*
Gemcitabine based (evaluable n = 145)	53 (37)	34 (47)	19 (26)	.008*
Bv (evaluable n = 157)	98 (62)	39 (55)	59 (69)	.07*
CPIs	39 (18)	4 (3)	35 (36)	<.001*
Before allo-HCT	5 (8.5)	0	5 (14.7)	
Clinical trial participation	71 (46)	42 (55)	29 (38)	.02*
Data missing	62	42	20	.066* †
Allo-HCT performed	59 (28)	25 (22)	34 (35)	.03*
Data missing	5	4	1	
Type of allo-HCT				.320* †
MRD	14 (24)	6 (24)	8 (23.5)	
MUD	30 (51)	15 (60)	15 (44)	
Haploidentical	8 (13)	1 (4)	7 (21)	
Cord blood	7 (12)	3 (12)	4 (12)	
Clinical outcome with allo-HCT				
TRM at 100 d after allo-HCT	5 (8.5)	3 (12)	2 (6)	.641* †
Complications related to allo-HCT				.343* †
aGVHD	15 (25)	4 (16)	11 (32)	
cGVHD	7 (12)	2 (8)	5 (15)	
Infection	5 (8.5)	3 (12)	2 (6)	

MRD, matched related donor; MUD, matched unrelated donor.
*χ^2 test.
†Fisher's exact test.

or progression between patients. Multivariate Cox regression analysis was used to determine predictors of OS by cohort from the time of auto-HCT relapse. Effect of Bv/CPIs and allo-HCT treatment after auto-HCT relapse was analyzed as a time-dependent covariate, using extended Kaplan Meier curves. These curves estimate the survival experience of 2 hypothetical patients: 1 who received treatment earliest and 1 who never got the intervention. The *P* value was based on Mantel-Byar test. Patients with missing data were removed from the analysis of the corresponding variables.

Results

Patient characteristics

Six hundred and fourteen patients who received auto-HCT from 2005 to 2016 were identified. Two hundred fifteen (35%) patients relapsed after auto-HCT. Among those, 118 were from cohort 1 and 97 were from cohort 2. The median age at auto-HCT, time from diagnosis to transplant, and time from transplant to relapse were similar in cohorts 1 and 2 (Table 1). The disease status before transplant, as assessed by CT, differed between the 2 cohorts, with fewer patients in complete response (CR; 24% vs 45%) and more patients in partial response (PR; 64% vs 46%) in cohort 1 than in cohort 2, respectively ($P = .002$). However, as assessed by positron emission tomographic (PET) scan in evaluable patients, the disease status before transplant did not differ significantly between the 2 cohorts: 39% vs 45% were PET negative in cohorts 1 and 2, respectively ($P = .37$). The median number of lines of therapy after relapse from auto-HCT were 2 each in cohorts 1 (range, 0-13) and 2 (range, 0-7) ($P = .07$). Thirty-nine (55%) patients in cohort 1 and 59 (69%) patients in cohort 2 received Bv as a subsequent therapy after auto-HCT ($P = .07$). Similarly, 4 (3%) patients in cohort 1 vs 35 (36%) patients in cohort 2 received CPIs as a subsequent therapy after auto-HCT relapse ($P \leq .001$; Table 2).

Survival outcomes

At a median follow-up of 5 years after auto-HCT relapse, 38% of patients were alive in the entire group (Figure 1A): 32% in cohort 1 and 50.5% in cohort 2 ($P = .01$; Figure 1B). The proportion of patients alive at 5-year follow-up from time of auto-HCT relapse, using left truncation analysis was 30% and not reached in cohorts 1 and 2, respectively ($P = .0076$; Figure 1C). We then evaluated the effect of time to relapse from auto-HCT (<1 year vs >1 year) on postrelapse OS. The 5-year OS was 32% and 57% in patients who relapsed in ≤1 year or >1 year from auto-HCT, respectively ($P = .003$; Figure 1D).

In multivariate analysis for post–auto-HCT relapse overall survival (OS), cohort 1 vs 2 (hazard ratio [HR], 2.3; 95% confidence interval [CI], 1.14-4.60; $P = .02$), age at auto-HCT (HR, 1.48; 95% CI, 1.18-1.87; $P \leq .001$) time to relapse from auto-HCT (HR, 0.59; 95% CI, 0.47-74; $P \leq .0001$), progressive disease (PD) vs CR at auto-HCT (HR, 2.86; 95% CI, 0.97-8.44; $P = .05$), and stable disease (SD) vs CR (HR, 8.82; 95% CI, 1.06-73.3; $P = .04$) retained independent prognostic significance for OS. Bv/CPI treatment after auto-HCT (HR, 0.90; 95% CI, 0.49-1.67; $P = .75$) or allo-HCT after auto-HCT relapse (HR, 0.86; 95%, CI; 0.42-1.67;

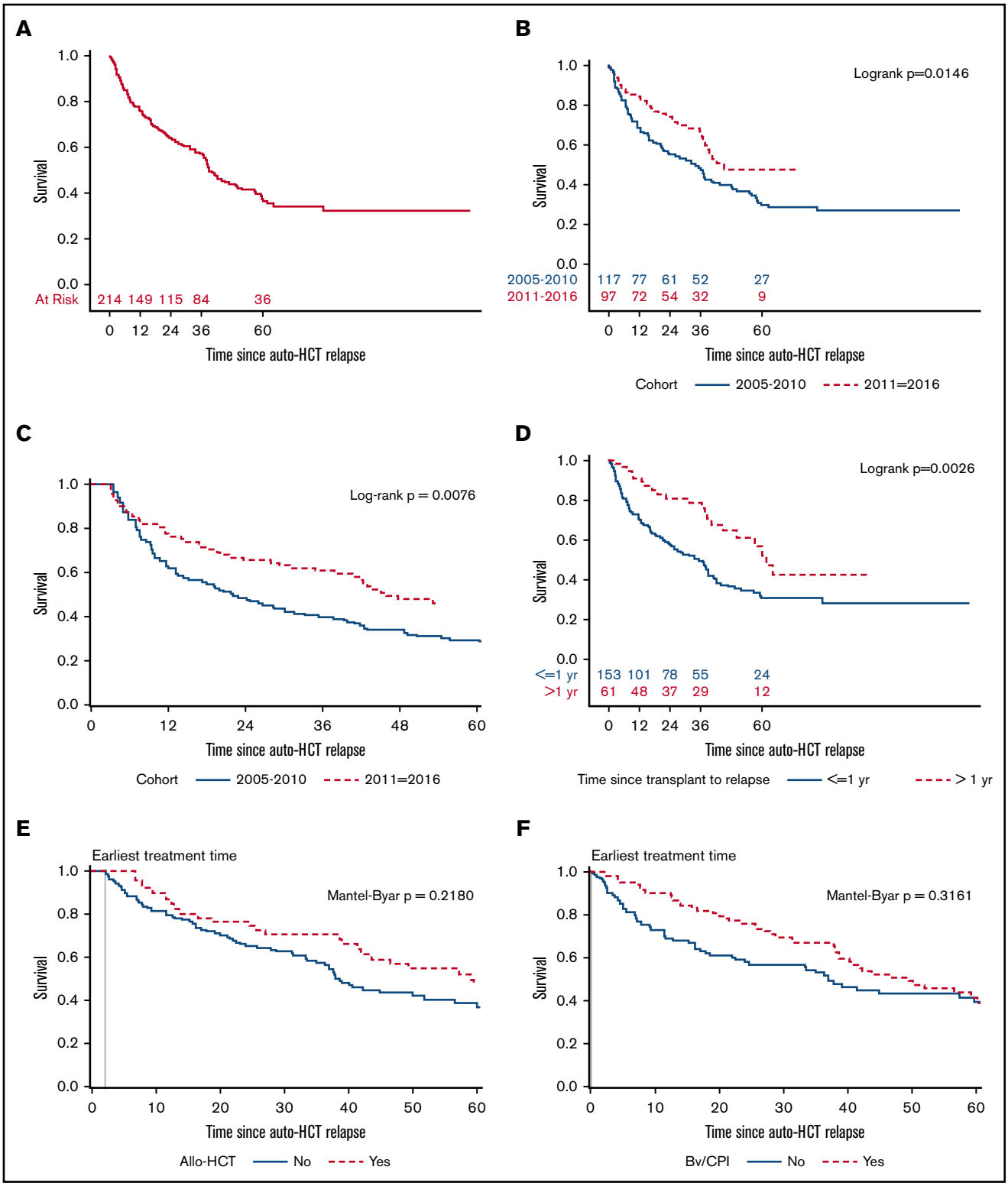

Figure 1. OS after post–auto-HCT relapse. Data were collected for the entire group (A); comparing cohorts 1 and 2 (B); comparing cohorts 1 and 2 using left truncation (C); comparing time to relapse after auto-HCT, <1 year vs >1 year (D); comparing patients who underwent allo-HCT or did not, as a time-dependent variable (E); and comparing patients who received Bv and/or CPIs vs neither (F).

Table 3. Multivariate Cox regression analysis for cHL overall survival

Description	Point estimate	Lower 95% CI	Upper 95% CI	*P*
Cohort 1 vs cohort 2	2.300	1.148	4.606	.02
After Bv or CPI after relapse	0.908	0.492	1.679	.7594
After allo-HCT after relapse	0.860	0.426	1.738	.6742
Age at auto-HCT*	1.489	1.183	1.875	.0007
Time to relapse from auto-HCT†	0.596	0.474	0.749	<.0001
ECOG PS at auto-HCT 1-2 vs 0	1.222	0.663	2.252	.5198
Disease status at auto-HCT				
PD vs CR	2.862	0.970	8.445	.0569
PR vs CR	0.837	0.420	1.670	.6143
SD vs CR	8.822	1.062	73.308	.0439

ECOG PS, Eastern Cooperative Oncology Group performance status.
*Age was used as a continuous covariate. The coefficient for age is per each 10-year increase in age after relapse.
†Transplant-to-relapse time was used as a continuous covariate. The coefficient from transplant to relapse was per each doubling of the elapsed time.

$P = .67$) as a time-dependent covariate did not show a significant effect on OS in multivariate analysis (Figure 1E-F; Table 3).

Regimens given after auto-HCT relapse

Overall, 98 (45%) patients received Bv, with a median time from relapse to Bv of 1.7 months (range, 0-98.5), overall response rate (ORR) of 71% (CR rate, 32%), and median PFS of 7.3 months. Thirty-nine (18%) patients received CPIs, with a median time from relapse to CPI of 13.9 months (range, 0.4-114), ORR of 74% (CR rate, 29%), and median PFS of 9.0 months. Overall, 5 (8.5%) patients received CPIs before allo-HCT. All of these patients were from cohort 2. Gemcitabine-based chemotherapy was administered in 53 (25%) patients after auto-HCT relapse, with a median time from relapse to gemcitabine of 8.8 months (range, 0.1-114), ORR of 68% (CR rate, 20%), and median PFS of 4.5 months. Thirty-one (14%) patients received an anthracycline-based regimen, with a median time from relapse to anthracycline therapy of 7.7 months (range, 0-79), ORR of 60% (CR rate of 17%), and median PFS of 4.6 months (Figure 2).

Allo-HCT after auto-HCT relapse

Fifty-nine (27%) patients received allo-HCT after auto-HCT relapse: 25 (22%) from cohort 1 and 34 (35%) from cohort 2 ($P = .03$). Overall, 14 patients (24%) received matched related donor (n = 6 [24%] cohort 1, n = 8 [24%] cohort 2), 30 patients (51%) received matched unrelated donor (n = 15 [60%] cohort 1; n = 15 [44%] cohort 2), 8 patients (14%) received haploidentical (n = 1 [4%] cohort 1; n = 7 [21%] cohort 2) and 7 patients (12%) received cord blood (n = 3 [12%] cohort 1; n = 4 [12%] cohort 2) allo-HCT. Transplant-related mortality (TRM) within 100 days after allo-HCT was observed in 3 (12%) and 2 (6%) patients from cohorts 1 and 2, respectively ($P = .64$). Acute graft-versus-host disease (aGVHD) was observed in 15 (25%) patients: 4 (16%) from cohort 1 and 11 (32%) from cohort 2. Chronic GVHD (cGVHD) was observed in 7 (12%) patients overall: 2 (8%) from cohort 1 and 5 (15%) from cohort 2 (Table 2).

Median PFS after allo-HCT was 14.2 months (95% CI; 7.4 to not reached; Figure 2E). After allo-HCT outcome as a time-dependent covariate in multivariate analysis showed lower HR for mortality, but it was not statistically significant (HR, 0.86; 95% CI, 0.42-1.67; $P = .67$).

Of the 5 patients who received CPIs before allo-HCT, 2 had aGVHD and 1 of those had TRM within 100 days of allo-HCT. Median time from CPIs to allo-HCT was 1 month (range, 1-4.1). One patient had disease progression 6.2 months after allo-HCT, whereas the remaining patients were in remission at the time of last follow-up.

Discussion

Our analysis supports our hypothesis that clinical outcomes for cHL patients who relapse after auto-HCT have significantly improved in recent years. This improvement is most likely related to the integration of novel therapies and more accessibility of allo-HCT in eligible patients, potentially in part because of the more widespread application of haploidentical allo-HCT.

Historically, the outcome of cHL patients who relapse or progress within a year of auto-HCT has been dismal, with median survival ~1 to 1.5 years.[6,14] In this group of patients, Bv in a phase II pivotal study showed an objective response rate (ORR) of 75%, including a CR rate of 34%.[14] The median PFS observed was 6.5 months, and 89% were alive at 1-year follow-up. These outcomes were significantly better than those in traditional salvage chemotherapy regimen trials given in the same era, such as the combination regimen of gemcitabine, liposomal doxorubicin, and vinorelbine.[15] Similarly, in our study, Bv given in the post–auto-HCT relapse setting showed an ORR of 71% (CR; 32%) with a median PFS of 7.3 months. Among the patients who received Bv, a larger proportion were from cohort 2, likely contributing in part to the improved outcome of cohort 2.

For patients who progress after auto-HCT and Bv, the outcome has been poor, with a median survival of only 3.5 months in 1 study.[16] cHL has a unique immune escape mechanism characterized by amplification of 9p24.1 and consequent upregulation of PD-L1 and -L2, making cHL particularly susceptible to CPIs such as the PD-1 inhibitors nivolumab and pembrolizumab.[17] Nivolumab was tested in a trial of 23 relapsed/refractory cHL patients, including 78% who progressed after auto-HCT and Bv. In that study, nivolumab achieved

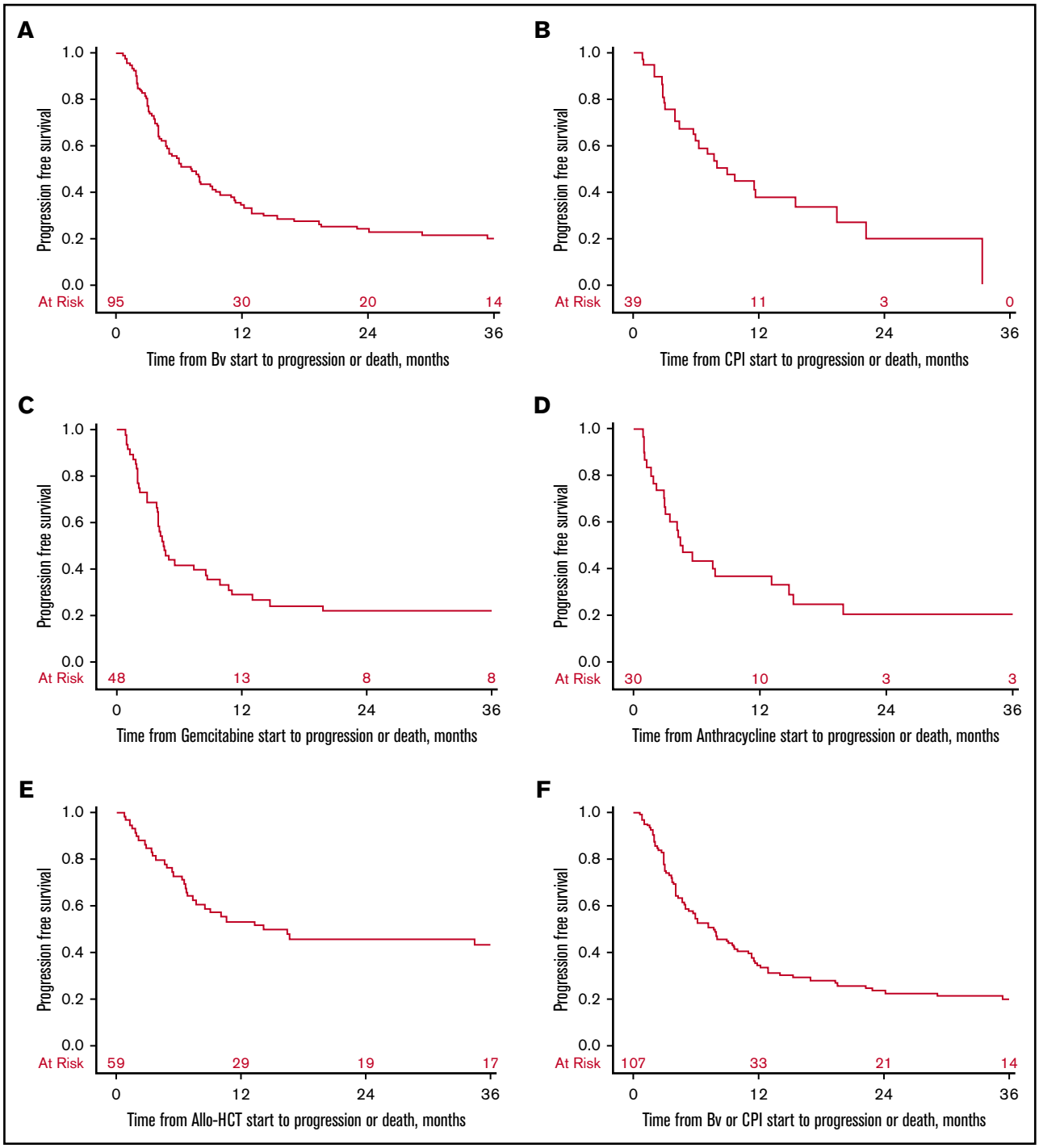

Figure 2. PFS after post–auto-HCT relapse. Data were collected after treatment with Bv (A), CPIs (B), gemcitabine-based chemotherapy regimens (C), anthracycline-based chemotherapy regimens (D), allogeneic hematopoietic stem cell transplantation (E), and Bv and/or CPIs (F).

an ORR of 87% and a CR of 17%.[11] Short-term PFS reported in that study at the 24-week follow-up was 86%. In our study, 39 (18%) patients received CPIs after auto-HCT relapse, with 90% being in cohort 2. Most of these patients received CPIs relatively late, with the median time from post–auto-HCT relapse to initiation of the drug being 13.9 months. ORR observed with CPIs was 74% (CR 28%) with median PFS of 9 months. Complementing previous studies, our analysis from this multicenter collaboration in the real-world setting demonstrates that immune modulation via CPIs can improve outcomes of poor-risk patients with multiply-relapsed or refractory cHL.

Historically, allo-HCT has been used as a treatment strategy in patients with multiply-relapsed refractory cHL. However, the overall landscape regarding the role, timing, and extent of use of allo-HCT

in cHL continues to change. A recent meta-analysis concluded that the outcome of allo-HCT for cHL has improved in recent years because of better supportive care, the use of reduced-intensity conditioning regimens, increased accessibility, and improved outcome with alternative (haploidentical) transplantation.[18] Further supporting that notion, the Center for International Blood and Marrow Transplant Research (CIBMTR) recently conducted a study focusing on 596 patients who underwent a reduced intensity allo-HCT for HL from 2008 through 2016. In that study, 3-year PFS was 34% to 38% with a 1-year nonrelapse mortality (NRM) rate of 6% to 11%, depending on donor source. Three-year OS was 63%, a dramatic improvement compared with pre-2010 studies, in which NRM in excess of 50% was reported in some series.[19,20] In our study, we found that a higher proportion of patients from cohort 2 (35%) underwent allo-HCT compared with the number from cohort 1 (22%; $P = .03$). Moreover, a higher proportion of patients from cohort 2 (21%) compared with the proportion from cohort 1 (4%) received haploidentical allo-HCT. One can postulate that with the availability of better salvage regimens and the use of haploidentical donors, more patients respond and become eligible for allo-HCT.

However, at the same time that improved outcomes were seen with allo-HCT, there appeared to be a shift toward decreased use of allo-HCT for HL with the availability of Bv and CPIs. This finding is illustrated by the relatively small proportion of patients proceeding to allo-HCT after CPI treatment on the CheckMate 205 study with nivolumab (18% of 243 patients) and the KEYNOTE-087 study with pembrolizumab (4.8% of 219 patients).[12,21] In addition, from 2012 through 2017, the number of cases of allo-HCT performed for HL in the United States reported to the CIBMTR decreased by ~45% (Marcelo Pasquini and Jeanette Carreras, CIBMTR, oral communication, 26 March 2019). This change may be related in part to concerns about increased risk of severe GVHD when allo-HCT is sequenced after CPI therapy, and/or to a perception that long-term disease control after failure of auto-HCT can now be attained without the use of allo-HCT, because of the availability of Bv, CPIs, other novel agents and anti-CD30 chimeric antigen receptor therapy. Although it is possible that this perception will eventually prove to be true, studies with long-term follow-up have yet to validate it, and caution should be exercised when advising against a potentially curative option with a long track record (allo-HCT), particularly in younger patients in whom NRM would be expected to be low.

In subgroup analyses, we evaluated response rate and PFS with novel therapies (Bv and CPIs) and chemotherapy (gemcitabine or anthracycline)-based salvage regimens after auto-HCT relapse. We observed better response rates (in the range of 70% to 75% vs 60% to 68%) and improved PFS (range, 7.0-9.0 months vs 4.5 months) with novel therapies compared with chemotherapy-based salvage regimens, respectively. However, long-term disease control was comparable with PFS of ~20% at 3-year follow-up across all salvage regimens. Our analysis supports the notion that for long-term disease control in high-risk cHL patients who progress after auto-HCT, allo-HCT should continue to play a significant role.[22]

We acknowledge the limitation of our retrospective analysis, including the possibilities of inherent selection bias, incomplete capture of all relevant data in 100% of patients, and limited follow-up in small proportions of evaluated patients. A significant proportion of patients had SD or PD before auto-HCT, which one could argue may have contributed to an increased risk of relapse; however, the proportion of patients with SD/PD were comparable in the 2 cohorts. After adjusting for the disease status at auto-HCT in the multivariate analysis, the inclusion of these patients did not substantively affect the conclusions. A sensitivity analysis removing those patients also did not qualitatively change the estimated cohort effect.

In summary, the outcomes of cHL patients who experience relapse after auto-HCT appear to have improved considerably in recent years, owing to new treatment options (such as Bv and CPIs), increased use of allo-HCT, and better supportive care. Future research should focus on earlier integration of novel therapies for patients with refractory disease to improve outcomes further.

Authorship

Contributions: T.B. was responsible for the study design and methodology and drafted the original manuscript; N.E. designed the study; A.S. was responsible for the methodology and statistical analysis; S.B., J.V., G.G., N.S., A.R.S., and R.D.P. were responsible for data curation; S.A., M.H., N.N.S., and A.F.C. contributed patients and edited the manuscript; and T.S.F. designed the study and methodology, contributed patients, and edited the manuscript.

Conflict-of-interest disclosure: T.S.F. has received prior research funding from Millennium, Kyowa, TG Therapeutics, Portola, and Curis; has served as a consultant for Genentech, Adaptive Biotechnologies, AbbVie, and Verastem; and has been a speaker for Seattle Genetics, Sanofi, Genentech, AstraZeneca, Celgene, and Adaptive Biotechnologies. N.N.S. has received honoraria and/or travel support from Incyte, Celgene, and Lentigen Technology; has served on scientific advisory boards for Kite, Celgene, and Cellectar; and has received institutional research support for clinical trials from BMS and Miltenyi Biotec. A.F.C. has served as a speaker for Seattle Genetics. The remaining authors declare no competing financial interests.

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