REGULAR ARTICLE

blood advances

Phase 2 study of PD-1 blockade following autologous transplantation for patients with AML ineligible for allogeneic transplant

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Key Points

- Pembrolizumab after autologous transplant is safe and effective, with low nonrelapse mortality and 2-year OS and LFS and OS of 68% and 48%.
- In patients with nonfavorable risk AML, OS was comparable for propensity score–matched patients receiving an allogeneic transplant.

Allogeneic transplant remains the best postremission therapy for patients with nonfavorable risk acute myeloid leukemia (AML). However, some patients are ineligible because of psychosocial barriers, such as lack of appropriate caregiver support. We hypothesized that immune checkpoint inhibition after autologous transplant might represent effective postremission therapy in such patients. We conducted a phase 2 study of autologous transplantation followed by administration of pembrolizumab (8 cycles starting day +1). Twenty patients with nonfavorable AML in complete remission were treated (median age, 64 years; CR1, 80%); 55% were non-White and adverse-risk AML was present in 40%. Treatment was well tolerated, with only 1 nonrelapse death. Immune-related adverse events occurred in 9 patients. After a median follow-up of 80 months, 14 patients remain alive, with 10 patients in continuous remission. The estimated 2-year LFS was 48.4%, which met the primary end point of 2-year LFS >25%; the 2-year overall survival (OS), nonrelapse mortality, and cumulative incidences of relapse were 68%, 5%, and 46%, respectively. In comparison with a propensity score–matched cohort group of patients with AML receiving allogeneic transplant, the 3-year OS was similar (73% vs 76%). Patients in the study had inferior LFS (51% vs 75%) but superior postrelapse survival (45% vs 14%). In conclusion, programmed cell death protein–1 blockade after autologous transplant is a safe and effective alternative postremission strategy in patients with nonfavorable risk AML who are ineligible for allogeneic transplant, a context in which there is significant unmet need. This trial was registered at www.clinicaltrials.gov as #NCT02771197.

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Protocol and inquiries for data requests for collaborative purposes are available on request from the corresponding author, Scott R. Solomon (ssolomon@bmtga.com).

The full-text version of this article contains a data supplement.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. Treatment with modern chemotherapy regimens often induces complete remission (CR), but a majority of patients will ultimately relapse and die of their disease. Results with conventional cytarabine-based postremission therapy are unsatisfactory for the three-quarters of patients with AML who do not fall in the favorable cytogenetic or molecular risk category. Five-year cumulative incidence of relapse (CIR) after high-dose cytarabine is >60% in intermediate-risk AML and 90% in poor-risk AML.[1] Allogeneic (allo) transplantation remains the best postremission therapy for patients with nonfavorable risk AML, secondary to the potent graft-versus-leukemia effect of donor immune cells. Unfortunately, some patients may be ineligible for allogeneic transplant because of age, comorbidities, psychosocial barriers (eg, lack of appropriate caregiver support), or unavailability of a suitable donor. Indeed, only a small proportion of patients who may benefit from allotransplantation have historically accessed it.[2-5]

Autologous stem cell transplantation (autotransplant) has been evaluated as an alternative postremission therapy for patients with AML.[6-14] In the context of poor-risk AML, autotransplant appears to provide little benefit over conventional chemotherapy resulting in dismal outcomes with 2-year overall survival (OS) of <20%.[7] However, autotransplant may be a viable postremission therapy for certain patients with intermediate-risk AML, such as those with normal karyotype and wild-type (WT) FLT3.[11,14] However, for the vast majority of patients with nonfavorable risk AML, autotransplant appears to offer no significant survival benefit over conventional consolidation chemotherapy and is no longer considered a recommended postremission therapy.[15]

Therefore, alternative strategies, such as those that promote autologous antileukemic immunity, are clearly needed. Inhibition of the programmed cell death protein-1 (PD-1) pathway is an effective immunotherapeutic anticancer strategy for a number of malignancies. We hypothesized that PD-1 blockade after autotransplant might represent an alternative postremission strategy in patients with nonfavorable risk AML. In order to mitigate the effects of naturally occurring regulatory T-cell populations, which are often increased in patients with cancer, we chose to test the effects of PD-1 blockade in the context of a lymphodepleting chemotherapy regimen consisting of fludarabine and melphalan followed by autologous stem cell rescue.

To this end, we initiated a phase 2 study in which patients with nonfavorable risk AML deemed ineligible for allotransplant received autotransplant followed by administration of short-course pembrolizumab (autopembro), initiated early after stem cell infusion and continued for ~6 months. We hypothesized that this strategy would be well tolerated and may mitigate the high risk of relapse associated with conventional high-dose cytarabine-based consolidation in this group of patients.

Patients and methods

Eligibility and enrollment

The study was approved by the Institutional Review Board at Northside Hospital, clinically registered as NCT02771197, and was performed in accordance with the Declaration of Helsinki. Patients were eligible for inclusion if they were aged between 18 and 78 years, had nonfavorable risk AML in morphologic CR or with incomplete blood count recovery (CRi) and were ineligible for allotransplant for any reason. Patients with nonfavorable risk AML were further stratified to be at intermediate and adverse risk (supplemental Table 1). CR was defined as the absence of residual leukemia based on morphology, flow cytometry, cytogenetics, and fluorescence in situ hybridization (FISH) studies. Molecular measurable residual disease (MRD) was permitted; however, the measurement of pretransplant MRD was not dictated by the study. MRD was defined as the presence of positive flow cytometric, cytogenetic or FISH or molecular (eg, next-generation sequencing and polymerase chain reaction) in patients who otherwise met the definition of morphological CR/CRi.

Patients beyond CR1 were eligible regardless of the cytogenetic or molecular risk category. Patients with CR1 were excluded if their AML was associated with either (i) core-binding factor (t[8;21], inv [16]) with WT c-kit, (ii) double CCAAT/enhancer-binding protein–α mutations, or (iii) mutant NPM1 with WT FLT3. Before study entry, patients should have completed at least 1 cycle of postremission therapy and collected ≥2 × 10^6/kg $CD34^+$ cells. Stem cell mobilization occurred before study entry and thus the mobilization strategy was not study mandated. Six patients, who otherwise met study eligibility, were excluded from study entry because of inability to collect a sufficient stem cell dose.

Treatment plan

The treatment protocol is depicted in Figure 1. Transplant conditioning consisted of fludarabine 30 mg/m^2 per day on days −4, −3, and −2 and melphalan on day −1 (180 mg/m^2 for patients aged ≤60 years [myeloablative] and 140 mg/m^2 for those aged >60 years [reduced intensity]), followed by autotransplant. Posttransplant pembrolizumab 200 mg per dose was initiated on day +1 and continued every 3 weeks with 8 doses. Other posttransplant maintenance therapies, such as hypomethylating agents or FLT3 inhibitors, were not permitted.

Standard prophylaxis, including a quinolone antibiotic, fluconazole or alternative broad-spectrum azole antifungal agent, and acyclovir, was started on day 0. Filgrastim 5 μg/kg was given daily starting day 6 and continued until neutrophil engraftment. Standard pneumocystis prophylaxis was started on day 30 and continued at least 6 months after transplant. Chemotherapy was dosed based on ideal body weight (IBW) for patients who weighed from 100% to

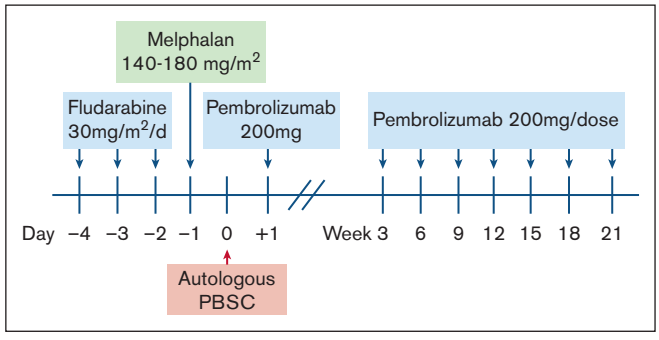

Figure 1. Treatment schema. PBSC, peripheral blood stem cells.

130% of their IBW. For patients who weighed <100% of their IBW, dosing was based on the actual body weight. For patients who weighed >130% of their IBW, dosing was based on the adjusted IBW (adjusted IBW = IBW + [(0.25) × (actual body weight − IBW)]). Oral cryotherapy was used during melphalan administration to reduce stomatitis.

Study end points

The primary end point of the study was to estimate the 2-year leukemia-free survival (LFS). Secondary end points included an estimate of 2-year OS, CIR, and nonrelapse mortality (NRM) as well as the frequency of treatment-emergent adverse events attributable to the use of posttransplant pembrolizumab.

Comparison with the control cohort of patients with nonfavorable risk AML receiving standard allo transplant conditioning

Transplant outcomes for patients receiving autotransplant followed by pembrolizumab were compared with those of a contemporaneous cohort of 112 consecutive patients with nonfavorable risk AML receiving allotransplant in CR1 or later CRs. Included patients were those who could have met inclusion criteria for the study (age, performance status, organ function, and AML risk criteria). This cohort included patients receiving allotransplant from a matched-related, unrelated, or haploidentical donor and either marrow or peripheral blood stem cells as the graft source. To obtain a control group with similar baseline characteristics, propensity score matching (PSM) was performed as detailed in "Statistical Analysis." Out of a total of 112 allocontrols, 63 were matched to 19 (of the 20) patients receiving autotransplant and pembrolizumab.

Statistical analysis

The study was powered to demonstrate a significant improvement in the 2-year LFS above the expected value of ~25% in patients who did not receive transplantation and were with nonfavorable risk AML.[1] We framed the objective to the hypotheses H0: $S(t) = 0.25$ vs H1: $S(t) > 0.25$ for $t = 2$, in which $S(t)$ denotes the LFS probability at t. The 1-sided Wald test at 5% significance level was used to test the hypotheses. Given that the 2-year vital status was collected for each enrolled patient, the size of 20 patients yielded the power of ~76%, assuming an actual 2-year LFS of 50%.

In the comparative evaluation with allotransplant, we used the propensity matching method to obtain a control group of similar characteristic distributions. A logistic regression model for type of transplant was fitted to the data of 20 patients in the study (autopembro) and 112 patients receiving allotransplants, and included the following variables: age (continuous), AML risk category (adverse or intermediate), status before bone marrow transplantation (CR1 or CR2/3), hematopoietic cell transplant comorbidity index (0-2, 3-5, or ≥6), and the year of transplant (2016-2018 or 2019-2021). The probabilities of receiving autotransplant were computed based on the logistic regression model for all the patients and used as the propensity scores. After examining propensity score distributions, we decided to use 0.01 as the difference criterion to search for controls matching with each study participant. This difference in criterion was ~11.5% of the propensity score standard deviation in 20 study participants. A maximum of 5 matched controls were allowed for each study participant. We failed to find any matched control for 1 study participant. Of the remaining 19, a total of 63 PSM controls were found including 1 matched control found for each of 4 participants, 2 matched controls found for each of 2 participants, 3 matched controls found for each of 4 participants, 4 matched controls found for each of 2 participants, and 5 matched controls found for each of 7 study participants. The statistical analyses were performed based on the matched-pair cohort (N = 82).

The patient characteristics were compared between 2 transplant groups using the Wilcoxon rank sum test for the continuous variables and Fisher exact test for the categorical variables. OS and LFS were estimated using the Kaplan-Meier method. The cumulative incidence, accounting for competing risks, was estimated for NRM and CIR. Comparisons of OS and LFS among different transplant groups were evaluated using the log-rank test, whereas comparisons of the cumulative incidences were compared among different transplant groups using the Gray test.

The marginal Cox model was used to evaluate effect for type of transplant adjusting for correlation in matched pairs. The robust sandwich covariance matrix was used to estimate precision of the hazard ratio (HR). The assumption of proportional hazards was tested by adding a time-dependent covariate. The proportionality failed for the marginal Cox model for LFS, and the transplant effect was modeled as piece-wise constant HRs in this model. Determination of cut point on time was guided by Akaike information criterion (AIC) on a few selected time points including 6, 9, 12, and 18 months. We reported 2-sided P values in data analysis, and P values $< .05$ were considered as significant. All statistical analyses were performed using the Statistical Analysis System software (version 9.4, the SAS Institute, Cary, NC).

Results

Patient characteristics

Twenty patients were treated from January 2017 to July 2021. Baseline patient characteristics are shown in Table 1 and include a median age of 64 years (range 26-75), Karnofsky performance status < 80 in 30% of the patients, hematopoietic cell transplant comorbidity index ≥ 3 in 85%, and non-White race in 55% (45%, Black race). AML characteristics included adverse risk in 40%, secondary/treatment-related in 20%, CR1 status in 80%, and pre-BMT MRD^+ in 30%.

Treatment compliance, regimen-related toxicity, and NRM

Fifteen of 20 patients (75%) completed the planned 8 doses of pembrolizumab after transplantation. Five patients discontinued treatment early because of disease progression (2 patients), toxicity (2 patients) or patient choice (1 patient). Treatment was overall well tolerated in only 1 nonrelapse-related death (myocardial infarction at 9 months after transplantation in a patient with significant pretransplant coronary artery disease). Estimated 2-year NRM was 5%. Infections included bacterial infections in 5 patients, cytomegaloviral viremia in 2 patients, localized varicella-zoster virus infection in 1 patient, and human herpesvirus 6 reactivation in 1 patient. Grade 3 nonhematologic toxicities are listed in Table 2 and include nausea or vomiting (25%), diarrhea (25%), hypertension (20%), and stomatitis or esophagitis (15%). There

Table 1. Pretransplant patient and disease characteristics

	Overall population			PSM group		
	Autopembro	Allotransplant		Autopembro	Allotransplant	
	(N = 20)	(N = 112)	*P* value	(N = 19)	(N = 63)	*P* value
Age, median (range)	63.5 (26-75)	55 (18-75)	.12	64 (26-75)	59 (22-74)	.42
Male sex	7 (35%)	66 (59%)	.05	7 (37%)	39 (62%)	.07
Race						
Non-Hispanic White	9 (45%)	77 (69%)		8 (42%)	41 (65%)	
Hispanic White	0 (0%)	8 (7%)		0 (0%)	5 (8%)	
Black	9 (45%)	16 (14%)	.02	9 (48%)	12 (19%)	.03
Asian	1 (5%)	9 (8%)		1 (5%)	5 (8%)	
American Indian/native Alaskan	1 (5%)	1 (1%)		1 (5%)	0 (0%)	
Unknown	0 (0%)	1 (1%)				
KPS						
60-80	19 (95%)	98 (87%)	.47	18 (95%)	56 (89%)	.67
90	1 (5%)	14 (13%)		1 (5%)	7 (11%)	
HCT-CI						
0-2	3 (15%)	39 (35%)		3 (16%)	13 (21%)	
3-5	14 (70%)	53 (47%)	.14	14 (74%)	39 (62%)	.75
≥6	3 (15%)	20 (18%)		2 (11%)	11 (17%)	
Patient CMV status						
Positive	15 (75%)	88 (79%)	.77	15 (79%)	49 (78%)	1.00
Negative	5 (25%)	24 (21%)		4 (21%)	14 (22%)	
AML risk category						
Adverse	8 (40%)	41 (37%)	.72	8 (42%)	23 (37%)	.79
Intermediate	12 (60%)	71 (63%)		11 (58%)	40 (63%)	
Time from diagnosis to transplant, median (range)	156 (94-1530)	135.5 (67-6182)	.09	152 (94-1505)	148 (72-6182)	.40
Time from CR to transplant*, median (range)	108 (48-356)	83.5 (20-589)	.02	105 (48-356)	91 (21-589)	.18
Induction						
FLAG-ida/CLAG-ida	10 (50%)	84 (75%)		10 (53%)	44 (70%)	
7 + 3	6 (30%)	14 (12%)		5 (26%)	8 (13%)	
CPX-351	2 (10%)	8 (7%)	.10	2 (11%)	6 (10%)	.38
FLAG	2 (10%)	3 (3%)		2 (11%)	2 (3%)	
HMA/venetoclax	0 (0%)	2 (2%)		0 (0%)	2 (3%)	
HMA	0 (0%)	1 (1%)		0 (0%)	1 (2%)	
Consolidation						
HiDAC	18 (90%)	76 (68%)		17 (89%)	41 (65%)	
HMA	2 (10%)	21 (19%)		2 (11%)	11 (17%)	
HMA/venetoclax	0 (0%)	4 (3%)	.61	0 (0%)	4 (6%)	.59
Clo-Cy	0 (0%)	1 (1%)		0 (0%)	1 (2%)	
Vyxeos	0 (0%)	2 (2%)		0 (0%)	1 (2%)	
None	0 (0%)	8 (7%)		0 (0%)	5 (8%)	
Consolidation(no. of cycles), median (range)	2 (1-7)	1 (0-16)	.02	2 (1-7)	1.5 (0-16)	.13
FLT3-ITD mutated (yes)	3 (15%)	34 (30%)	.19	3 (16%)	16 (25%)	.54
FLT3-TKD (yes)	2 (20%)	7 (6%)	.63	2 (11%)	2 (3%)	.23
NPM1 (yes)	2 (10%)	31 (28%)	.16	2 (11%)	16 (25%)	.22
IDH1/2 (yes)	6 (30%)	27 (24%)	.58	6 (32%)	13 (21%)	.36

Clo-Cy, clofarabine, cytarabine; CLAG-ida, cladribine, cytarabine, G-CSF, idarubicin; CMV, cytomegalovirus; FLAG-ida, fludarabine, cytarabine, G-CSF, idarubicin; HAPLO, haploidentical donor; HCT-CI, hematopoietic cell transplant comorbidity index; HiDAC, high dose cytarabine; HMA, hypomethylating agent; ITD, intertandem duplication; KPS, Karnofsky performance status; MLL, mixed lineage leukemia; MRD, measurable residual disease; auto, autologous; MUD, matched unrelated donor; Myelo, myeloablative; nonmyelo, nonmyeloablative; RIC, reduced intensity conditioning; TKD, tyrosine kinase domain; CPX-351, liposomal daunorubicin and cytarabine.

*Time from CR to transplant is initiated from most recent CR before transplant.

Table 1 (continued)

	Overall population			PSM group		
	Autopembro (N = 20)	Allotransplant (N = 112)	*P* value	Autopembro (N = 19)	Allotransplant (N = 63)	*P* value
MLL (yes)	2 (10%)	5 (4%)	.29	2 (11%)	5 (8%)	.66
ASXL1/RUNX1/TP53 (yes)	5 (25%)	23 (21%)	.77	5 (26%)	12 (19%)	.53
C-KIT^{+} CBF (yes)	2 (10%)	6 (5%)	.35	2 (11%)	3 (5%)	.33
−7/del7q (yes)	2 (10%)	10 (9%)	1.00	2 (11%)	6 (10%)	1.00
Complex karyotype (yes)	2 (10%)	16 (14%)	1.00	2 (11%)	9 (14%)	1.00
Secondary AML (yes)	3 (15%)	15 (13%)	.74	3 (16%)	8 (13%)	.71
Therapy-related AML (yes)	1 (5%)	8 (7%)	1.00	1 (5%)	5 (8%)	1.00
Pretransplant status						
CR1	16 (80%)	94 (84%)	.74	16 (84%)	53 (84%)	1.00
CR2/3	4 (20%)	18 (16%)		3 (16%)	10 (16%)	
MRD^{+} at PBMT						
Yes	6 (30%)	28 (25%)		6 (32%)	17 (27%)	
No	14 (70%)	76 (68%)	.65	13 (68%)	42 (67%)	.73
Unknown	0 (0%)	8 (7%)		0 (0%)	4 (6%)	
Donor type						
AUTO	20 (100%)	0 (0%)		19 (100%)	0 (0%)	
Matched related donor	0 (0%)	28 (25%)	< .001	0 (0%)	16 (25%)	< .001
MUD	0 (0%)	26 (23%)		0 (0%)	16 (25%)	
HAPLO	0 (0%)	58 (52%)		0 (0%)	31 (49%)	
Intensity						
Myelo	9 (45%)	58 (52%)		9 (47%)	29 (46%)	
RIC	11 (55%)	34 (30%)	.03	10 (53%)	20 (32%)	.04
Nonmyelo	0 (0%)	20 (18%)		0 (0%)	14 (22%)	
Y of transplant						
2017-2018	11 (55%)	46 (41%)	.33	10 (53%)	29 (46%)	.79
2019-2021	9 (45%)	66 (59%)		9 (47%)	34 (54%)	
No. of survivors	14	78		14	49	
Survivor follow-up (mo), median (range)	36.9 (10.9-58.6)	35.0 (13.8-70.2)	.69	36.9 (10.9-58.6)	36.9 (14.1-69.2)	.80

Clo-Cy, clofarabine, cytarabine; CLAG-ida, cladribine, cytarabine, G-CSF, idarubicin; CMV, cytomegalovirus; FLAG-ida, fludarabine, cytarabine, G-CSF, idarubicin; HAPLO, haploidentical donor; HCT-CI, hematopoietic cell transplant comorbidity index; HiDAC, high dose cytarabine; HMA, hypomethylating agent; ITD, intertandem duplication; KPS, Karnofsky performance status; MLL, mixed lineage leukemia; MRD, measurable residual disease; auto, autologous; MUD, matched unrelated donor; Myelo, myeloablative; nonmyelo, nonmyeloablative; RIC, reduced intensity conditioning; TKD, tyrosine kinase domain; CPX-351, liposomal daunorubicin and cytarabine.

*Time from CR to transplant is initiated from most recent CR before transplant.

were no treatment-emergent grade 4 or 5 nonhematologic toxicities. Possible immune-related adverse events (IrAEs) included 3 cases of hypothyroidism, 2 cases of colitis, and 1 case each of pneumonitis, transverse myelitis, inflammatory dermatitis, and seronegative arthritis. Treatment of IrAEs included methylprednisolone in 2 cases (pneumonitis and myelitis), budesonide in 1 case (colitis), and topical steroids in 1 patient.

Relapse, LFS, and OS

After a median follow-up of 37 months (range 11-59 months), 14 patients remained alive, with 10 patients in continuous remission. Estimated 2-year and 3-year LFS was 48.4% (95% CI, 25.4-68.2), which met the primary end point of 2-year LFS >25%. Two-year OS, NRM, and CIR were 68%, 5%, and 46%, respectively (Figure 2A). Relapse, LFS, and OS were similar in patients with adverse vs intermediate AML risk (Figure 2B-D). Pretransplant MRD status also had no significant impact on relapse and survival (supplemental Figure 2). Patients developing possible pembrolizumab-associated IrAEs (n = 9) had a statistically nonsignificant improvement in LFS and OS (supplemental Figure 1). Of the 9 patients who relapsed after transplantation, 2 patients subsequently received an allotransplant. In these cases, the psychosocial barriers that did not originally permit transplant were resolved.

Propensity score–matched comparison of autopembro and allotransplant recipients

To better assess the relative value of autopembro transplant compared with that of allotransplant, PSM was applied to match 63 allotransplant controls to 19 patients who received autopembro. A comparison of patient before transplant and disease characteristics in both the original allotransplant control group (112

Table 2. Grade 3 nonhematologic toxicity

	Autopembro (N = 20)
Diarrhea	5 (25%)
Nausea/vomiting	5 (25%)
Hypertension	4 (20%)
Stomatitis/esophagitis	3 (15%)
Abdominal pain	2 (10%)
Fatigue	2 (10%)
Hypokalemia	2 (10%)
Increased aspartate aminotransferase (AST)	2 (10%)
Increased bilirubin	2 (10%)
Colitis	1 (5%)
Hiccups	1 (5%)
Hypokalemia	1 (5%)
Hyponatremia	1 (5%)
Hypotension	1 (5%)
Hypoxia	1 (5%)
Increased alanine aminotransferase (ALT)	1 (5%)
Pneumonitis	1 (5%)
Small bowel obstruction	1 (5%)
Syncope	1 (5%)

contemporaneous consecutive patients with AML receiving allotransplant in CR1 or later CRs) and PSM cohorts (19 autopembro vs 63 matched allotransplant recipients) are listed in Table 1. Autopembro recipients were more likely to be of Black race (48% vs 19%) and female (63% vs 38%) than allotransplant recipients but were otherwise similar in regard to baseline patient and disease characteristics.

Compared with PSM-paired allotransplant controls, the 3-year OS, LFS, NRM, and CIR in autopembro recipients were 73% vs 76% ($P = .76$), 51% vs 75% ($P = .06$), 5% vs 14% ($P = .35$), and 11% vs 44% ($P = .003$) in autopembro vs allotransplant recipients, respectively (Figure 3). Postrelapse survival was better after autopembro (45% vs 14%; $P = .04$; supplemental Figure 2). Using the marginal Cox model to evaluate the effect of transplant type, adjusting for correlation in matched pairs, there were no differences in the OS (HR 1.17; $P = .74$) between patients who received autopembro and those who received allotransplant, whereas LFS (HR, 4.06; $P = .01$) and relapse (HR, 4.15; $P < .01$) favored allotransplant (Table 3).

Discussion

We report the outcomes of a prospective phase 2 study of autotransplant followed by short-course pembrolizumab maintenance therapy as postremission consolidation in patients with nonfavorable

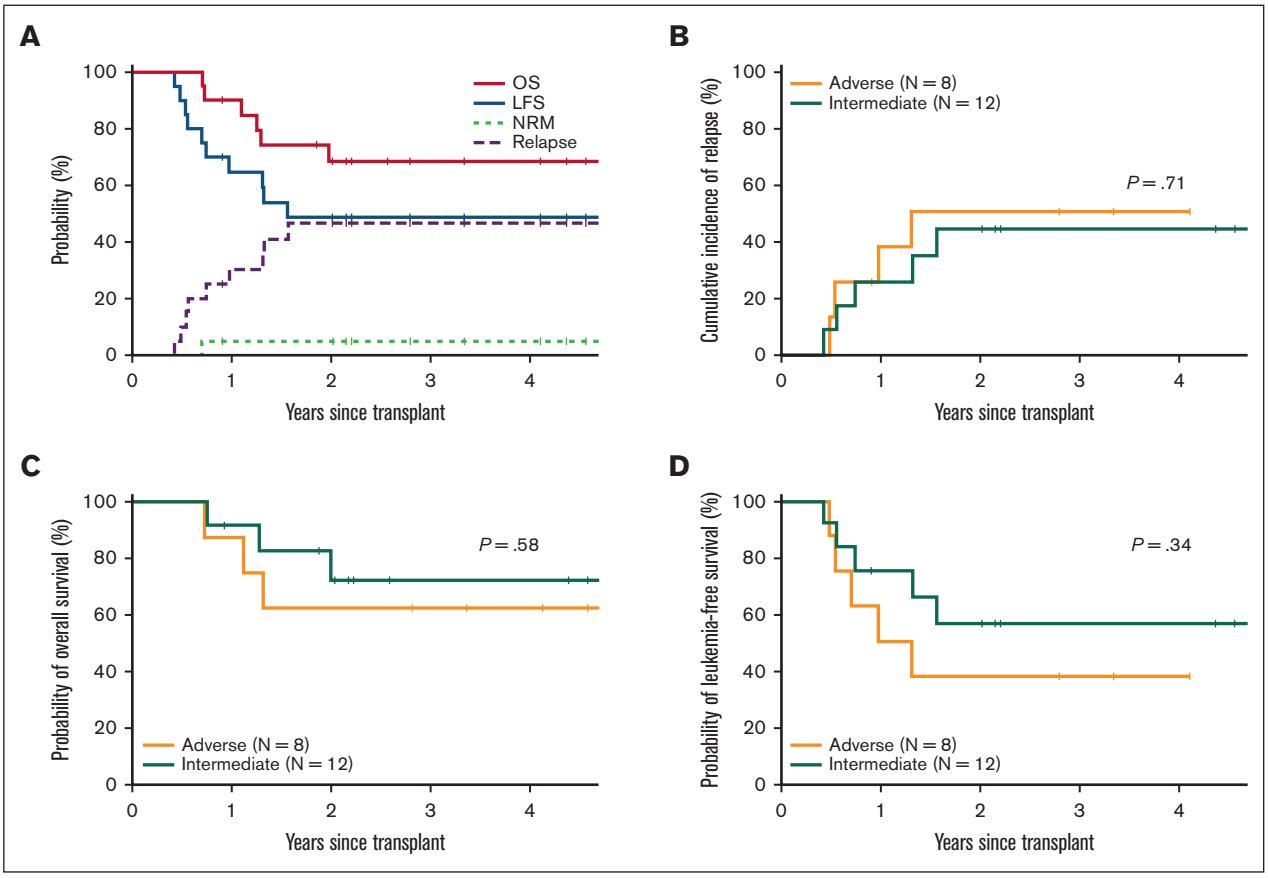

Figure 2. OS, LFS, NRM, and CIR for AML recipients of autotransplant with posttransplant pembrolizumab. (A-D) CIR, OS, and LFS based on the AML risk category.

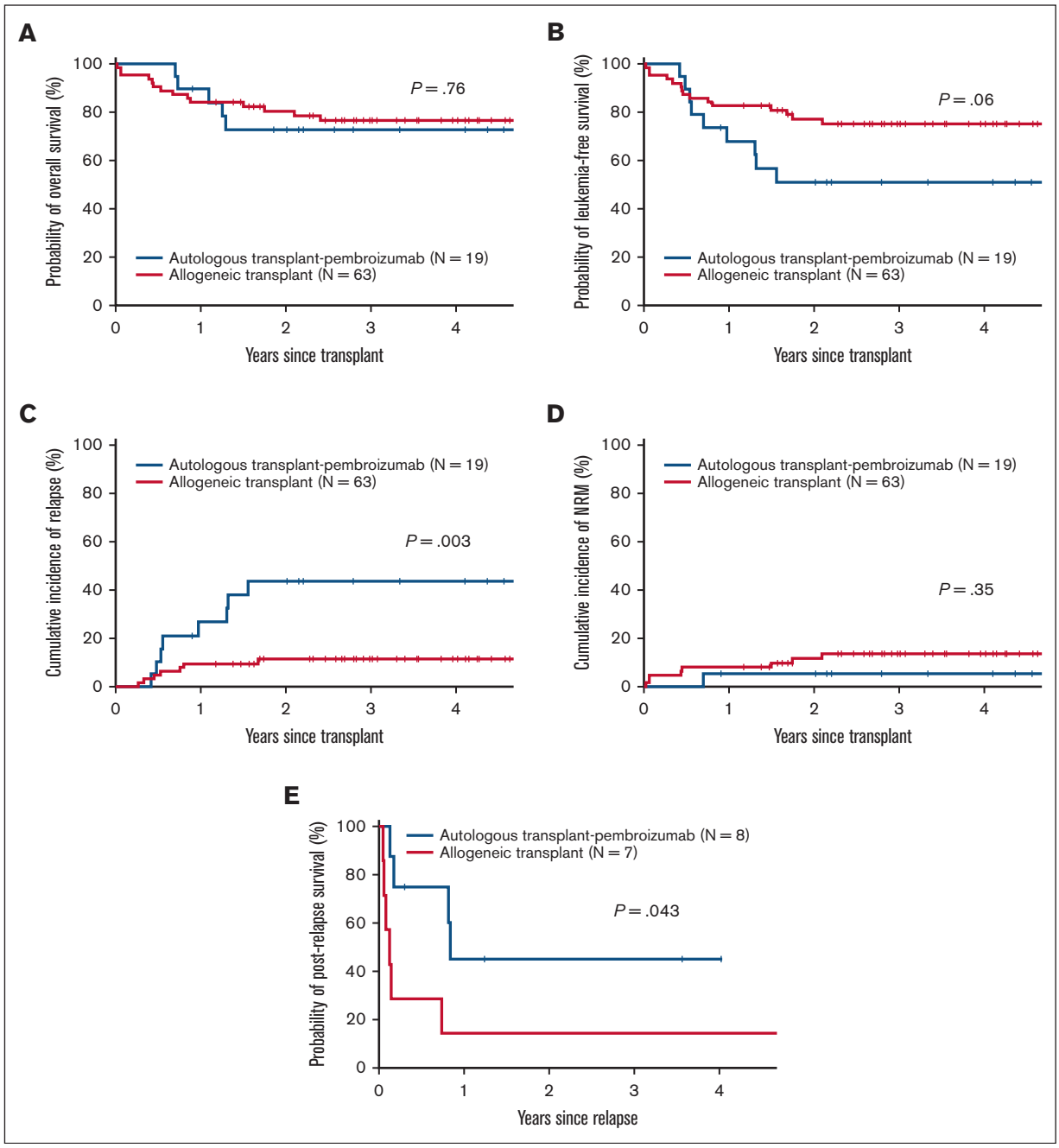

Figure 3. Comparison of OS, LFS, NRM, and CIR for AML recipients between recipients of autotransplant followed by pembrolizumab vs propensity score–matched recipients of allotransplant: OS (A), LFS (B), CIR (C), NRM (D), and postrelapse survival (E).

risk AML not eligible for allotransplant. We show that this strategy is feasible and safe, with acceptable rates of regimen-related toxicity and low NRM. Two-year LFS was 48.4%, which met the primary end point of 2-year LFS >25% (expected with cytarabine-based consolidation in patients with nonfavorable risk AML). Furthermore, there was no difference in posttransplant survival when autopembro transplant recipients were compared with a PSM-paired control group of patients with nonfavorable risk AML receiving allotransplant at our institution. Although relapse risk was lower after allotransplant, postrelapse survival was superior in patients who received autopembro.

Although allotransplant remains the standard-of-care approach for consolidation after transplantation in patients with nonfavorable risk AML, not all patients are eligible for this treatment because of multiple reasons, such as age, presence of comorbidities, lack of appropriate psychosocial resources, or absence of a suitable donor. Historically, patients with nonfavorable risk have

Table 3. Estimated HRs for autopembro vs allotransplant in marginal Cox models

Outcome	Effect	HR	95% CI	*P* value
OS	Autopembro vs allotransplant	1.17	0.45–3.05	.740
LFS	Autolpembro vs allotransplant within 6 mo	0.79	0.20–3.15	.740
	Autopembro vs allotransplant beyond 6 mo	4.06	1.37–12.09	.012
Relapse	Autopembro vs allotransplant	4.15	1.47–11.70	.007
NRM	Autopembro vs allotransplant	0.46	0.05–4.30	.500

demonstrated poor outcomes after conventional chemotherapy consolidation strategies, with an expected 2-year LFS between 20% and 25%[1,16] because of high relapse risk. More recently, modest improvements in LFS in transplant-ineligible patients have been shown with the use of maintenance therapy with oral azacitidine.[16] However, there is clearly an unmet need for new strategies in this patient population at high risk.

It is also noteworthy that the autopembro cohort included a significantly higher proportion of Black patients with AML compared with the allotransplant control group. Non-White patients with AML have historically faced significantly greater barriers to the receipt of allotransplant.[17-19] Recently, much of this disparity has been addressed by greater donor availability through greater use of alternative donor sources, such as haploidentical donors or cord blood. However, published data from our center has demonstrated that despite near universal donor availability, being of Black race remains to be a significant barrier to the receipt of allotransplant, with 1 major obstacle being a lack of sufficient caregiver support.[20] Therefore, alternative postremission approaches are needed to help address this persistent health disparity for Black patients with AML.

The efficacy of allotransplant in AML is largely due to the graft-versus-leukemia effect, in which donor immune effector cells target tumor antigens on recipient leukemia cells. Theoretically, the expression of leukemia-specific antigens could also render them susceptible to recognition and killing using autologous cytotoxic T cells as well. However, spontaneous rejection of established cancers rarely, if ever, occurs, in part because of negative regulatory mechanisms used by the tumor and its microenvironment. One such inhibitory mechanism is upregulation of PD ligand 1 (PD-L1), expressed on tumor cells, which binds to PD-1 on activated T cells.[21] A wide variety of tumor cells express PD-L1, including AML cells.[22] PD-1/PD-L1 engagement results in diminished antitumor T-cell responses and correlates with poor outcome in cancers in murine and human.[23-26] The PD-1 molecule has been recognized as a hallmark for cell exhaustion, and PD-1 expressing antigen-specific T cells are dysfunctional in cytokine production and proliferation upon antigen restimulation.[27]

Another important immunoevasion strategy used by cancer cells involves the increased frequency of regulatory T cells (Tregs) observed in patients with cancer. These naturally occurring immunosuppressive T-cell populations have been negatively correlated with anticancer immunity in AML and other cancers.[28-31] Depletion of Tregs in a number of transplantable cancer models results in significantly enhanced antitumor immune responses and control of tumor progression. In AML, several groups have observed elevated Treg frequencies in the blood and marrow of patients with AML, and this appears to correlate negatively with chemotherapy response and survival.[30,31] In murine AML models, depletion of Tregs alone or in combination with PD-L1 blockade resulted in enhanced antileukemic T-cell responses.[32,33]

In order to address both suppressive factors in tumor environment that inhibit the function of a sufficient immune response (ie, Tregs) as well as defeated immune effector components that are unable to control tumor growth (ie, PD-1 expressing T cells), we attempted to overcome these obstacles through a combination of lymphodepletion (high-dose chemotherapy and autologous transplantation) and anti-PD1 blockade. Chemotherapy-induced lymphodepletion may enhance the effectiveness of immunotherapy though several different mechanisms, including increased availability of immune stimulatory cytokines and the creation of an environment conducive to disruption of T-cell tolerance.[34] Adoptive cellular therapy after lymphodepleting chemotherapy is known to cause regression of established tumors in murine model[35-37] and clinical studies,[38,39] highlighting the importance of modulating the host environment through lymphodepletion. In this study, we used a high-dose chemotherapy approach to achieve both myeloablation for optimal leukemia debulking and lymphodepletion to both disrupt immunologic tolerance mechanisms and favor the induction of antileukemia immune responses.

In this analysis, patients with nonfavorable risk AML achieved a 3-year OS and LFS of 66% and 48%, respectively. When compared with the control group of the QUAZAR AML-001 study, which represents a useful comparator of the results of conventional chemotherapy alone in a clinical trial population, our results compare favorably (3-year OS and LFS of ~30% and 20%, respectively in that study).[16] We also show that the OS after an autopembro approach is statistically similar to that seen after allotransplant in a contemporaneously treated control cohort at our institution receiving similar patient care practices and supportive care algorithms. Furthermore, relapse risk and survival after autopembro was similar in European Leukemia Net (ELN) patients with adverse vs intermediate-risk AML, suggesting that the patients with highest risk AML may derive the greatest benefit from PD-1 blockade. Finally, the suggestion of improved posttransplant outcomes in patients experiencing pembrolizumab-related IrAEs points to the importance of PD-1 inhibition in the efficacy of the autopembro treatment approach.

The major limitation of this study relates to its small sample size, which limits the power to detect statistical differences and makes subset investigations challenging. Furthermore, this analysis has limitation because of the lack of correlative studies, which could better define the role of PD-1 blockade in the antileukemic efficacy of this protocol. Ultimately, the findings of this small study will need to be validated in a larger, multicenter prospective study. In

addition, such a study could further elucidate mechanisms of action, predictors of response, and correlation of response with IrAEs. Ideally, future studies will test the effect of extended pembrolizumab dosing as well as the inclusion of potentially synergistic agents (eg, hypomethylating agents) in the hopes of further delaying leukemic relapse and improving outcomes for this patient population at high risk.

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Authorship

Contribution: S.R.S. designed the research; S.R.S., M.S., L.E.M.J., H.K.H, L.B-R. and A.B. treated patients; C.G. K.C.J. and S.B. collected the data; S.R.S. and X.Z. analyzed and interpreted data; X.Z. performed the statistical analysis; S.R.S. wrote the manuscript; and all authors revised and approved the final version of the manuscript.

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