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Analysis

Healthcare Utilization is High in Adult Patients Relapsing after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Disease relapse is the leading cause of death for patients with acute leukemia (AL) and myelodysplastic syndrome (MDS) who undergo allogeneic hematopoietic cell transplantation (HCT). Relapse post-HCT is associated with poor prognosis; however, inpatient healthcare utilization of this population is unknown. Here we describe survival, intensity of healthcare utilization, and characteristics associated with high resource use at the end of life (EOL). Adult patients with AL/MDS who underwent HCT at a large regional referral center with subsequent relapse between 2005 and 2015 were included in this retrospective study. We compared the distribution of demographic and clinical characteristics of patients as well as healthcare utilization over 2 years postrelapse and at EOL by postrelapse disease-directed therapeutic interventions. We created a composite score for EOL healthcare utilization intensity by summing the presence of any of the following criteria: death in the hospital, use of chemotherapy, emergency department, hospitalization, intensive care unit, intubation, cardiopulmonary resuscitation, or hemodialysis in the last month of life. Higher scores indicate more intense healthcare use at EOL. Multivariable linear regression analysis was used to determine variables (demographic characteristics, postrelapse treatment group, advance directives documentation, palliative care referral, time to relapse) associated with EOL healthcare utilization intensity. One hundred fifty-four patients were included; median age at relapse was 56 years (interquartile range [IQR], 39 to 63), 55% were men, 79% had AL, and median time from HCT to relapse was 6 months (IQR, 3 to 10). After relapse, 28% received supportive care only, 50% received chemotherapy only, and 22% received chemotherapy plus cell therapy (either donor lymphocyte infusion, second HCT, or donor lymphocyte infusion plus second HCT). With the exception of time until relapse and Karnofsky Performance Status, baseline characteristics (gender, age, race, graft-versus-host disease, year of treatment) did not significantly differ by postrelapse treatment group. One hundred thirty-six patients (88%) died within 2 years of relapse; survival differed significantly by postrelapse treatment group, with those receiving disease-directed treatment showing lower risk of death. Healthcare use in AL/MDS patients after post-HCT relapse was high overall, with 44% visiting the emergency department at least once (22% at least 2 times), 93% hospitalized (55% at least 2 times, 16% at least 5 times), and 38% using the intensive care unit (median length of stay 5, days; IQR, 3 to 10). Use was high even among those receiving only supportive care. For those patients who died, the mean intensity score for EOL healthcare use was 1.8 (standard deviation, 1.8). Most patients (70%) had a marker of high-intensity healthcare utilization at the EOL or died in hospital. In multivariable analysis, an increase in age (estimate -.03 (95% CI, -.06 to -.003) and having AL versus MDS were significantly associated with a decreased EOL healthcare intensity score; no other variables were associated with intensity of EOL healthcare use. Healthcare utilization after post-HCT relapse is associated with receipt of disease-directed therapy but remains high across all groups despite known poor prognosis. Interventions are needed to minimize nonbeneficial treatments and promote goal-concordant EOL care in this seriously ill patient population.

INTRODUCTION

Allogeneic hematopoietic cell transplant (HCT) is a mainstay of curative therapy for adults with acute leukemia (AL) and myelodysplastic syndrome (MDS). Advances in the management of HCT complications and reduced-intensity transplant approaches have expanded HCT to a broader cohort of

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patients, including those with impaired functional status or advanced age. However, post-HCT disease relapse continues to be a significant issue and remains the leading cause of death after HCT for adults with hematologic malignancies. Approximately 30% to 40% of adults with AL/MDS will relapse after HCT; these patients have a poor prognosis with median survival generally estimated at 6 months or less [1-10].

Relative to solid tumor cancers, hematologic malignancies are generally associated with underuse of palliative and hospice services and overuse of high-intensity treatments near the end of life (EOL) [11-16]. Rationales for this EOL pattern of care have been proposed, including the unpredictable pattern of clinical decline in patients with hematologic malignancies, clinicians' bias toward offering all possible treatments for these patients, and the small but finite possibility of cure for select patients [17]. Studies have similarly demonstrated that adults undergoing allogeneic HCT for hematologic malignancies use high levels of healthcare resources at EOL [18-22]. However, despite the exceedingly high risk of mortality in AL/MDS patients who relapse after allogeneic HCT, little data exist specifically examining the intensity of healthcare utilization broadly and at the EOL in this patient population, with the few existing studies reporting qualitative or limited data on small patient samples [23,24]. This retrospective observational study aims to fill this gap in the literature by analyzing healthcare utilization over time in AL/MDS patients who relapsed after allogeneic HCT in a large referral center in Northern California.

METHODS

Study Design

All adult patients (age ≥ 18 years at time of HCT) with acute myeloid leukemia (AML), acute lymphoblastic leukemia, or MDS who underwent first allogeneic HCT at Stanford University and subsequently experienced disease relapse between January 1, 2005 and December 31, 2015 were identified for inclusion. Stanford serves as a large-volume regional HCT referral center covering AL/MDS patients across a large swath of Northern California.

Patients who did not receive any postrelapse care at Stanford were excluded. Demographic and HCT characteristics were abstracted from an existing institutional research database maintained by the Stanford Blood & Marrow Transplant Program. All other variables were collected by detailed chart review of the electronic medical record, including electronically linked and scanned records from affiliated hospitals. Postrelapse therapies and hospital and emergency department (ED) admissions were evaluated over a 2-year time period after disease relapse. All included patients consented for Stanford Institutional Review Board–approved observational data collection and monitoring.

EOL Intensity Composite Score

In the subset of patients who died, we created an EOL intensity score using a composite of measures for defining the intensity of healthcare utilization at the EOL. No single validated intensity scoring system has yet been defined for EOL care in the blood cancer population; therefore, we used an approach similar to that utilized in prior work on EOL intensity in cancer patients [25-28]. One point was given for the presence of each of the following occurring within 30 days of death: use of chemotherapy, more than 1 hospitalization, more than 14 days of hospitalization, more than 1 ED visit, intensive care unit (ICU) admission, mechanical intubation, cardiopulmonary resuscitation, initiation of hemodialysis, or death in hospital. The total number of points was summed for an intensity score ranging from 0 to 9. A higher intensity score indicated greater usage of high-intensity treatment measures at EOL.

Statistical Analysis

We compared the distribution of demographic and clinical characteristics of patients by postrelapse disease-directed therapeutic interventions. Categorical variables were compared using chi-square or Fisher's exact tests; continuous variables were compared using the Kruskal-Wallis test. To compare healthcare use over 2 years postrelapse and at EOL, we grouped patients based on postrelapse disease-directed therapeutic interventions into 2 groups: those who received no treatment/supportive care and those who received any treatment (chemotherapy only or chemotherapy plus cell therapy). We compared the overall survival over 2 years postrelapse, by none/supportive care versus treatment, using Kaplan-Meier curves and conducted a multivariable Cox proportional hazards regression analysis to estimate the risk of death after relapse, adjusting for age at HCT, sex, race/ethnicity, primary diagnosis, graft-versus-host disease (none versus any), comorbidity (none versus any), year of HCT, months from HCT to relapse (<6 months versus ≥6 months), and Karnofsky Performance Status score (<90 versus ≥90). Time to death was calculated as the days from relapse until death; patients were censored at 2 years postrelapse or at the last follow-up date.

We also conducted multivariable linear regression analysis to determine if any variables were associated with EOL intensity of healthcare use. In addition to the variables included in the multivariable Cox proportional hazards regression model, we included presence of advanced directive documentation and referral to palliative care clinic or consultation service.

RESULTS

Between 2005 and 2015, 349 of 1249 adult patients (29%) with AL/MDS experienced relapse after their first allogeneic HCT. One hundred fifty-four of these patients continued to receive their hematologic or supportive care within the Stanford healthcare system and were included in our analytic cohort. Patient and HCT demographics are characterized in Table 1, stratified based on postrelapse disease-directed therapeutic interventions (none/supportive care only, chemotherapy only, chemotherapy plus additional cellular therapy). Median age at HCT was 55 years (interquartile range [IQR], 38 to 62), and median age at relapse was 56 years (IQR, 39 to 63). Fifty-five percent were men, 79% had AL, and median time from HCT to relapse was 6 months (IQR, 3 to 10). After post-HCT disease relapse, 28% did not receive any further disease-directed treatment, 50% received chemotherapy only, and 22% received chemotherapy plus additional cellular therapy (either donor lymphocyte infusion, n = 28; second HCT, n = 5; or donor lymphocyte infusion plus second HCT, n = 1). With the exception of time until relapse and Karnofsky Performance Status score ($P < .01$), there were no significant differences in demographic characteristics between postrelapse treatment groups; those receiving either chemotherapy or chemotherapy plus additional cellular therapy tended to have experienced a longer disease-free survival after initial HCT ($P < .01$).

One hundred thirty-six patients (88%) died within 2 years of post-HCT disease relapse; among these patients, median survival from the time of disease relapse was 4 months (IQR, 1 to 9). Two-year survival after relapse differed significantly by postrelapse treatment group (Figure 1), with patients who received treatment having a lower risk of death compared with patients who did not receive postrelapse treatment. Specifically, patients receiving treatment had an 81% less risk of death (hazard ratio, .19; 95% confidence interval, .11-.31) compared with patients receiving no disease-directed treatment.

Healthcare utilization in AL/MDS patients after post-HCT relapse is shown in Table 2. Overall use was high, with 68 patients (44%) visiting the ED at least once (34 [22%] at least 2 times, 9 [6%] at least 5 times), 141 patients (93%) hospitalized (85 [55%] at least 2 times, 24 [16%] at least 5 times), and 58 patients (38%) admitted to the ICU at least once (median length of ICU stay, 5 days; IQR, 3 to 10). Use of the ED and hospitalization were significantly higher in those receiving postrelapse treatment rather than supportive care only ($P < .001$), whereas ICU utilization was not associated with postrelapse treatment ($P = .16$).

Among the patients who died, the median intensity score for EOL healthcare use was 1 (IQR, 0 to 3), and the mean intensity score was 1.8 (standard deviation, 1.8) (Figure 2). Most patients (70%) had some high-intensity healthcare utilization toward the EOL. Over half of the patients (52%) died in a hospital setting, with 39% having a length of stay of at least 14 days in the last month of life. In multivariable regression analysis, an increase in age (estimate, −.03; 95% confidence interval,

Table 1
Demographic and Clinical Characteristics

		Treatment after Relapse		
Characteristic	All Patients (N = 154)	None (n = 43)	Chemotherapy Only (n = 77)	Chemotherapy Plus Cell Therapy* (n = 34)
Age at HCT, yr, median (IQR)	55 (38-62)	57 (48-63)	53 (38-62)	50 (27-61)
Age at relapse, yr, median (IQR)	56 (39-63)	57 (48-64)	54 (39-63)	52 (30-63)
Sex				
Male	85 (55.2)	22 (51.2)	43 (55.8)	20 (58.8)
Female	69 (44.8)	21 (48.8)	34 (44.2)	14 (41.2)
Race/ethnicity				
Hispanic	21 (13.6)	4 (9.3)	13 (16.9)	4 (11.8)
White	99 (64.3)	29 (67.4)	48 (62.3)	22 (64.7)
Asian	23 (14.9)	5 (11.6)	12 (15.6)	6 (17.7)
Black	2 (1.3)	2 (4.7)	0	0
Unknown/other	9 (8.8)	3 (7.0)	4 (5.2)	2 (5.9)
Primary diagnosis				
AML	89 (57.8)	26 (60.5)	41 (53.3)	22 (64.7)
Acute lymphoblastic leukemia	32 (20.8)	4 (9.3)	21 (27.3)	7 (20.6)
MDS	33 (21.4)	13 (30.2)	15 (19.5)	5 (14.7)
GVHD				
None	111 (72.1)	35 (81.4)	56 (72.7)	20 (58.8)
Limited	9 (5.8)	1 (2.3)	6 (7.8)	2 (5.9)
Extensive	34 (22.1)	7 (16.3)	15 (19.5)	12 (35.3)
Acute GVHD	47 (30.5)	14 (32.6)	27 (35.1)	6 (17.7)
Comorbidity index, mean (SD)	0.84 (1.3)	1.02 (1.6)	0.75 (1.1)	0.79 (1.4)
Karnofsky Performance Status score				
<90	28 (18.2)	10 (23.3)	17 (22.1)	1 (2.9)
≥90	114 (74.0)	29 (67.4)	54 (70.1)	31 (91.2)
Unknown	12 (7.8)	4 (9.3)	6 (7.8)	2 (5.9)
Year of HCT				
1999-2007	31 (20)	14 (33)	11 (14)	6 (18)
2008-2011	70 (45)	13 (30)	40 (52)	17 (50)
2012-2015	53 (34)	16 (37)	26 (34)	11 (32)
Months from HCT to relapse, median (IQR)	6 (3-10)	3 (1-6)	6 (3-11)	8 (5-24)
Time from HCT to relapse				
<6 mo	74 (48.0)	31 (72.1)	34 (44.2)	9 (26.5)
≥6 mo	80 (52.0)	12 (27.9)	43 (55.8)	25 (73.5)
Died	140 (90.9)	43 (100)	72 (93.5)	25 (73.5)
Months from relapse to death, median (IQR)	5 (1-9)	1 (1-2)	5 (2-9)	10 (7-13)
Location of death†				
Hospital	73 (52.1)	23 (53.4)	34 (47.2)	16 (64.0)
Hospice	42 (30.0)	14 (32.6)	23 (31.9)	5 (20.0)
Home w/o hospice	4 (2.9)	1 (2.3)	2 (2.8)	1 (4.0)
Unknown	21 (15.0)	5 (11.6)	13 (18.1)	3 (12.0)

Values are n (%) unless otherwise defined. GVHD indicates graft-versus host disease; SD, standard deviation.

* Chemotherapy plus cell therapy group: In addition to chemotherapy, 1 patient had both repeat HSCT and donor lymphocyte infusions, 5 had only repeat HCT, and 28 had only donor lymphocyte infusions.

† Percent based on number who died.

−.06 to −.003) and having acute lymphoblastic leukemia or AML versus MDS were significantly associated with a decreased EOL healthcare intensity score (Table 3).

DISCUSSION

The poor survival for our study population of AL/MDS patients relapsing after allogeneic HCT is similar to that identified in prior work in the field of allogeneic HCT [5-10]. Our study adds to the existing literature by detailing healthcare utilization and EOL healthcare intensity in this particularly vulnerable patient population. In our cohort, patients who received additional therapies (chemotherapy and/or additional cellular therapies) tended to have a longer disease-free interval after first HCT and higher Karnofsky Performance Status score, which may in general confer a modestly more favorable prognosis after post-HCT relapse [10] and may justify a more aggressive treatment course. In our population, there was in fact a survival advantage after receipt of further disease-directed therapy, although 2-year survival was still limited to 16% in patients receiving disease-directed treatment after relapse (chemotherapy ± additional cellular therapy).

Despite overall limited survival outcomes in this population relapsing after allogeneic HCT, healthcare utilization after disease relapse was high, with 44% visiting the ED, 92% hospitalized, and 38% spending hospital days in the ICU. These rates were particularly elevated among patients receiving postrelapse

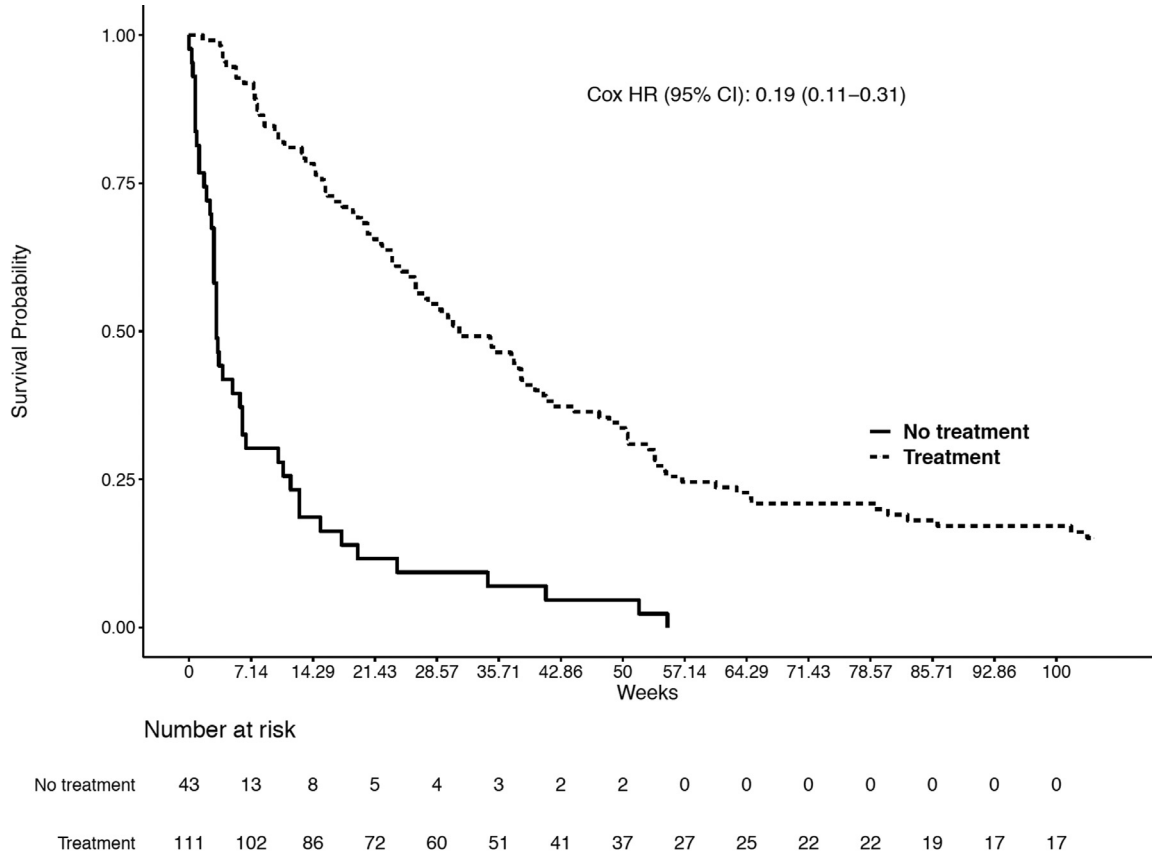

Figure 1. Survival probability by postrelapse treatment group.

Table 2
Healthcare Utilization after Relapse

		Disease-Directed Treatment after Relapse		
	All Patients (N = 154)	None (n = 43)	Any Treatment (n = 111)	*P*
ED visits				
0	86 (56)	38 (88)	48 (43)	<.001*
1	34 (22)	5 (12)	29 (26)	
≥2	34 (22)	0	34 (31)	
Hospitalizations				
0	13 (8)	8 (19)	5 (5)	<.001*
1	56 (36)	28 (65)	28 (25)	
≥2	85 (55)	7 (16)	78 (70)	
Length of stay, days				
Median (IQR)	28 (10-55)	6 (5-14)	36 (20-70)	<.001†
ICU stays				
0	96 (62)	32 (74)	64 (58)	.16*
1	43 (28)	9 (21)	34 (31)	
≥2	15 (10)	2 (5)	13 (12)	
Length of stay, days				
Median (IQR)	5 (3-10)	6 (3-9)	4.5 (3-10)	1.0†
Intubation	20 (13)	7 (16)	13 (12)	.44*
Cardiopulmonary resuscitation	7 (5)	3 (7)	4 (4)	.40*
Hemodialysis	8 (5)	1 (2)	7 (6)	.44*
Advance directives	82 (53)	26 (60)	56 (50)	.74‡
Palliative care consult	75 (49)	20 (47)	55 (50)	.12‡

Values are n (%) unless otherwise defined.
* Fisher's exact test.
† Wilcoxon rank-sum test.
‡ Chi-square statistic.

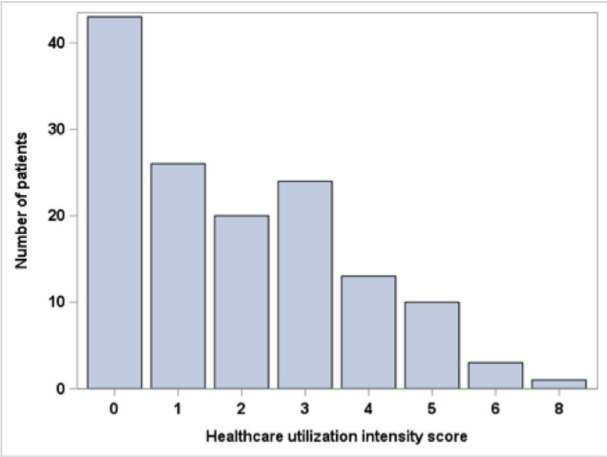

Figure 2. EOL healthcare utilization intensity composite score distribution.

disease-directed therapies; however, even among patients receiving supportive care alone, the rates of healthcare use were high. The ICU usage among this population of relapsed patients (26% admitted to the ICU with a median of 6 ICU days) is particularly concerning, as this likely represents nonbeneficial care for this population with 100% mortality by 14 months and median survival postrelapse of only 1 month.

Studies in solid tumor cancer patients reveal that healthcare intensity at the EOL is high overall, albeit lower than that seen in our population, particularly relating to death in the hospital [29-32]. We observed that patients used a median of 1 high-intensity healthcare service within 30 days of death. This usage was associated with age and underlying diagnosis, with patients of advancing age and those with acute lymphoblastic leukemia/AML versus MDS having decreased EOL care intensity. In the case of age, this trend may be a reflection of an enhanced awareness of EOL processes and wishes in older patient populations as well as a reduced willingness on the part of the patient or physicians to tolerate substantial treatment toxicity even in the hopes of achieving a durable remission or cure.

Our findings beg the question of what may be done to temper the use of nonbeneficial and expensive healthcare services among patients with exceedingly high morbidity and short life expectancy. Although we did not find that advance care planning or palliative care consultation independently impacted EOL healthcare intensity, others have demonstrated a multitude of benefits associated with palliative care consultation and advance care planning both near the EOL and concurrent with disease-directed treatment in both solid tumor and hematologic malignancy patients [18,20,33-40]. Various models have been proposed for integrating palliative care into the bone marrow transplant setting, particularly in pediatric populations [41]. Further investigation is warranted to determine if the timing, location, or content of palliative intervention modulates the effect on EOL care for this population.

Our study details the outcomes and healthcare utilization among AL/MDS patients relapsing at a single academic institution, which may not be generalizable to populations on a national scale or in other healthcare contexts. Patients who did not pursue postrelapse care at Stanford institutions were excluded from analysis because of a lack of accessibility of medical records. A substantial percentage of these patients (140 [72%] excluded for this reason) were a part of the Kaiser Permanente Healthcare System. Local norms are known to affect intensity of healthcare utilization at the EOL; therefore, the postrelapse and EOL course of those patients may differ from that presented here [42]. Our medical record abstraction of EOL care does not easily allow us to identify the intent of the care provided, which in some cases may have been palliative (eg, poorly controlled symptoms requiring ED visitation and hospital admission). We are aware that the care delivered to these patients at the EOL was provided without the benefit of

Table 3
Multivariable Regression Analysis of Characteristics Associated with Intensity of Healthcare Utilization at EOL (n = 128)

	Estimate	Standard Error	95% Confidence Interval	*P*
Age (128)*	−.03	.01	−.06 to −.003	.03
Sex: female (54) vs. male (74)	−.04	.36	−.76 to .68	.92
Race/ethnicity (vs. other/unknown (8))				
White non-Hispanic (79)	−.69	.73	−2.13 to .76	.91
Black non-Hispanic (2)	−1.06	1.54	-4.11 to 1.99	
Hispanic (18)	−.54	.81	−2.14 to 1.06	
Asian (21)	−.67	.80	−2.26 to .91	
Diagnosis (vs. MDS (26))				
Acute lymphoblastic leukemia (27)	−1.57	.62	−2.80 to −.33	.02
AML (75)	−1.18	.44	−2.05 to −.30	
GVHD: none (94) vs. any (34)	.51	.42	−.32 to 1.34	.23
Comorbidity (vs. 3+ (18))				
0 (74)	.46	.52	−.58 to 1.49	.65
1-2 (36)	.47	.56	−.64 to 1.58	
Karnofsky Performance Status score (<90 (27) vs. ≥90 (101))	.17	.43	−.69 to 1.03	.69
Year of HCT (vs. 2012 (47))				
1999-2007 (19)	−.41	.60	−1.59 to .78	.79
2008-2011 (62)	−.12	.38	−.88 to .63	
Months from HCT to relapse: <6 months (63) (vs. ≥6 months (65))	.14	.37	−.60 to .87	.72
No postrelapse disease-directed treatment (38) (vs. any treatment (90))	−.70	.38	−1.46 to .05	.07
Had palliative care consultation (74)	.46	.38	−.31 to 1.22	.24
Had advance care documentation (68)	−.16	.35	−.85 to .53	.65

* Values in parenthesis represent number of patients for each strata for the variable listed.

prophecy of their mortality, and their presumed prognosis at the time of care delivery may have been more optimistic than was achieved. Additionally, those patients with poor performance status or other illness at the time that disease relapse was diagnosed were unlikely to have received chemotherapy or additional cell therapies; this pre-existing illness may have conferred a poor prognosis irrespective of receipt of postrelapse disease-directed treatments and could in part account for the survival difference observed in that group. Given the lack of a nationwide shared electronic medical record, estimates for healthcare use may have been underestimated in some cases if patients received care at hospitals outside the Stanford-affiliated healthcare system. However, our results are similar to those of a larger population-based study of healthcare utilization in allogeneic HCT [18]. Additional investigation is required to assess whether the high-intensity care received by this population is concordant with documented advance care planning wishes.

In summary, most patients with AL/MDS who relapse after allogeneic HCT are exposed to high-intensity healthcare services after disease relapse and particularly at the EOL. Given the limited survival of AL/MDS patients who relapse after allogeneic HCT, even among those receiving additional chemotherapy and cellular therapy, patients should be encouraged to complete advance care planning and to have open conversations around goals of care in advance of therapy with their providers and families. Well-studied interventions are necessary to shift the current patterns of EOL care in this population to provide goal-concordant care and reduce use of nonbeneficial interventions that may prolong suffering without altering survival.

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REFERENCES

1. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. *Expert Rev Hematol*. 2010;3:429–441.
2. Arellano ML, Langston A, Winton E, Flowers CR, Waller EK. Treatment of relapsed acute leukemia after allogeneic transplantation: a single center experience. *Biol Blood Marrow Transplant*. 2007;13:116–123.
3. Oran B, Giralt S, Couriel D, et al. Treatment of AML and MDS relapsing after reduced-intensity conditioning and allogeneic hematopoietic stem cell transplantation. *Leukemia*. 2007;21:2540–2544.
4. Schmid C, Labopin M, Nagler A, et al. Treatment, risk factors, and outcome of adults with relapsed AML after reduced intensity conditioning for allogeneic stem cell transplantation. *Blood*. 2012;119:1599–1606.
5. Ganzel C, Sun Z, Cripe LD, et al. Very poor long-term survival in past and more recent studies for relapsed AML patients: the ECOG-ACRIN experience. *Am J Hematol*. 2018;93:1074–1081.
6. Pollyea DA, Artz AS, Stock W, et al. Outcomes of patients with AML and MDS who relapse or progress after reduced intensity allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2007;40:1027–1032.
7. Spyridonidis A, Labopin M, Schmid C, et al. Outcomes and prognostic factors of adults with acute lymphoblastic leukemia who relapse after allogeneic hematopoietic cell transplantation. An analysis on behalf of the Acute Leukemia Working Party of EBMT. *Leukemia*. 2012;26:1211–1217.
8. Poon LM, Hamdi A, Saliba R, et al. Outcomes of adults with acute lymphoblastic leukemia relapsing after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2013;19:1059–1064.
9. Matsumoto K, Yamamoto W, Ogusa E, Ishigatsubo Y, Kanamori H. Prognostic index for relapsed acute leukemia after allogeneic stem cell transplant. *Leuk Lymph*. 2014;55:2808–2812.
10. Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. *Biol Blood Marrow Transplant*. 2015;21:454–459.
11. Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? *J Clin Oncol*. 2008;26:3860–3866.
12. Fadul N, Elsayem A, Palmer JL, Zhang T, Braiteh F, Bruera E. Predictors of access to palliative care services among patients who died at a comprehensive cancer center. *J Palliat Med*. 2007;10:1146–1152.
13. Hui D, Kim S-H, Kwon JH, et al. Access to palliative care among patients treated at a comprehensive cancer center. *Oncologist*. 2012;17:1574–1580.
14. Sexauer A, Cheng MJ, Knight L, Riley AW, King L, Smith TJ. Patterns of hospice use in patients dying from hematologic malignancies. *J Palliat Med*. 2014;17:195–199.
15. Hui D, Didwaniya N, Vidal M, et al. Quality of end-of-life care in patients with hematologic malignancies: a retrospective cohort study. *Cancer*. 2014;120:1572–1578.
16. El-Jawahri AR, Abel GA, Steensma DP, et al. Health care utilization and end-of-life care for older patients with acute myeloid leukemia. *Cancer*. 2015;121:2840–2848.
17. Odejide OO, Salas Coronado DY, Watts CD, Wright AA, Abel GA. End-of-life care for blood cancers: a series of focus groups with hematologic oncologists. *J Oncol Pract*. 2014;10:e396–e403.
18. Cappell K, Sundaram V, Park A, et al. Advance directive utilization is associated with less aggressive end-of-life care in patients undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2018;24:1035–1040.
19. Johnston EE, Muffly L, Alvarez E, et al. End-of-life care intensity in patients undergoing allogeneic hematopoietic cell transplantation: a population-level analysis. *J Clin Oncol*. 2018;36:3023–3030.
20. Eckhert EE, Schoenbeck KL, Galligan D, McNey LM, Hwang J, Mannis GN. Advance care planning and end-of-life care for patients with hematologic malignancies who die after hematopoietic cell transplant. *Bone Marrow Transplant*. 2017;52:929–931.
21. Busemann C, Julich A, Buchhold B, et al. Clinical course and end-of-life care in patients who have died after allogeneic stem cell transplantation. *J Cancer Res Clin Oncol*. 2017;143:2067–2076.
22. Snaman JM, Talleur AC, Lu J, et al. Treatment intensity and symptom burden in hospitalized adolescent and young adult hematopoietic cell transplant recipients at the end of life. *Bone Marrow Transplant*. 2018;53:84–90.
23. Button EB, Gavin NC, Keogh SJ. Exploring palliative care provision for recipients of allogeneic hematopoietic stem cell transplantation who relapsed. *Oncol Nurs Forum*. 2014;41:370–381.
24. Lin RJ, Elko TA, Perales MA, et al. End-of-life care for older AML patients relapsing after allogeneic stem cell transplant at a dedicated cancer center. *Bone Marrow Transplant*. 2018;54:700–706.
25. Goodman N, Chang C, Fisher E, Wennberg JDM. Trends in cancer care near the end of life: a Dartmouth Atlas of health care brief. 2013. Available at: https://www.dartmouthaltas.org. Accessed October 8, 2018.
26. Luta X, Maessen M, Egger M, Stuck AE, Goodman D, Clough-Gorr KM. Measuring intensity of end of life care: a systematic review. *PLoS One*. 2015;10:e0123764.
27. Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. *J Clin Oncol*. 2003;21:1133–1138.
28. Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. *Int J Qual Health Care*. 2005;17:505–509.
29. Wang SY, Hall J, Pollack CE, et al. Trends in end-of-life cancer care in the Medicare program. *J Geriatr Oncol*. 2016;7:116–125.
30. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol*. 2004;22:315–321.
31. Morden NE, Chang CH, Jacobson JO, et al. End-of-life care for Medicare beneficiaries with cancer is highly intensive overall and varies widely. *Health Aff (Millwood)*. 2012;31:786–796.
32. Falchook AD, Dusetzina SB, Tian F, Basak R, Selvam N, Chen RC. Aggressive end-of-life care for metastatic cancer patients younger than age 65 years. *J Natl Cancer Inst*. 2017;109:1–6.
33. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733–742.
34. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA*. 2008;300:1665–1673.
35. Pedraza SL, Culp S, Knestrick M, Falkenstine E, Moss AH. Association of physician orders for life-sustaining treatment form use with end-of-life care quality metrics in patients with cancer. *J Oncol Pract*. 2017;13:e881–e888.
36. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol*. 2012;30:880–887.
37. De palma R, Fortuna D, Hegarty SE, Louis DZ, Melotti RM, Moro ML. Effectiveness of palliative care services: a population-based study of end-of-life care for cancer patients. *Palliat Med*. 2018;32:1344–1352.

38. Zhang B, Wright AA, Huskamp HA, et al. Health care costs in the last week of life: associations with end-of-life conversations. *Arch Intern Med*. 2009;99:261–266.
39. Garrido MM, Balboni TA, Maciejewski PK, Bao Y, Prigerson HG. Quality of life and cost of care at the end-of-life: the role of advance directives. *J Pain Symptom Manage*. 2015;49:828–835.
40. El-Jawahri A, Traeger L, Greer JA, et al. Effect of inpatient palliative care during hematopoietic stem-cell transplant on psychological distress 6 months after transplant: results of a randomized clinical trial. *J Clin Oncol*. 2017;35:3714–3721.
41. Levine DR, Baker JN, Wolfe J, Lehmann LE, Ullrich C. Strange bedfellows no more: how integrated stem-cell transplantation and palliative care programs can together improve end-of-life care. *J Oncol Pract*. 2017;13:569–577.
42. Walkey AJ, Barnato AE, Rinne ST, et al. Hospital variation in do-not-resuscitate orders and end-of-life healthcare use in the United States. *Ann Am Thorac Soc*. 2017;14:1485–1489.