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# Advance Directive Utilization Is Associated with Less Aggressive End-of-Life Care in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation

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### ABSTRACT

Allogeneic hematopoietic cell transplantation (HCT) is associated with significant morbidity and mortality, making advance care planning (ACP) and management especially important in this patient population. A paucity of data exists on the utilization of ACP among allogeneic HCT recipients and the relationship between ACP and intensity of healthcare utilization in these patients. We performed a retrospective review of patients receiving allogeneic HCT at our institution from 2008 to 2015 who had subsequently died after HCT. Documentation and timing of advance directive (AD) completion were abstracted from the electronic medical record. Outcomes of interest included use of intensive care unit (ICU) level of care at any time point after HCT, within 30 days of death, and within 14 days of death; use of mechanical ventilation at any time after HCT; and location of death. Univariate logistic regression was performed to explore associations between AD completion and each outcome. Of the 1031 patients who received allogeneic HCT during the study period, 422 decedents (41%) were included in the analysis. Forty-four percent had AD documentation before death. Most patients (69%) indicated that if terminally ill, they did not wish to be subjected to life-prolonging treatment attempts. Race/ethnicity was significantly associated with AD documentation, with non-Hispanic white patients documenting ADs more frequently (51%) compared with Hispanic (22%) or Asian patients (35%;  $P = .0007$ ). Patients with ADs were less likely to use the ICU during the transplant course (41% for patients with ADs versus 52% of patients without ADs;  $P = .03$ ) and also were less likely to receive mechanical ventilation at any point after transplantation (21% versus 37%,  $P < .001$ ). AD documentation was also associated with decreased ICU use at the end of life; relative to patients without ADs, patients with ADs were more likely to die at home or in hospital as opposed to in the ICU (odds ratio, .44; 95% confidence interval, .27 to .72). ACP remains underused in allogeneic HCT. Adoption of a systematic practice to standardize AD documentation as part of allogeneic HCT planning has the potential to significantly reduce ICU use and mechanical ventilation while improving quality of care at end of life in HCT recipients.

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### INTRODUCTION

Allogeneic hematopoietic cell transplant (HCT) represents the only curative option for many patients with high-risk and advanced hematologic malignancies but remains an intensive process with the potential for significant morbidity and mortality. HCT recipients are more likely to use

intensive healthcare services at end of life (EOL) and are less likely to die at home or under hospice care relative to patients receiving therapies for solid tumors [1-5]. Improving EOL care in HCT represents a priority for our patients and the greater HCT community to reduce patient suffering, minimize aggressive interventions, and reduce inappropriate healthcare resource utilization.

Advance care planning (ACP), the process by which an individual voluntarily outlines wishes and preferences for future EOL treatments, is an essential component of planning for high-quality EOL care [6]. ACP may be documented in standard advance directive (AD) forms that typically provide

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information regarding a future medical proxy in addition to guidance on preferences for life-sustaining treatments. The importance of ACP was highlighted in the 2014 Institute of Medicine consensus document on quality death and dying in the United States [7] and subsequently has been recognized by the Centers for Medicare & Medicaid Services as an important and billable medical service. ACP and early palliative care integration in solid tumor cancer patients is associated with multiple benefits, including reductions in hospitalizations, fewer ineffective and burdensome high-intensity medical treatments at EOL, improved quality of life, and increased life span [8-12].

Relatively little is known about the usage of ACP in the allogeneic HCT population and the impact of ACP on HCT outcomes and quality of death in this population. Studies conducted in the early 2000s demonstrated that ACP documentation in the medical chart of adult HCT recipients was low at 39% to 50%, although a larger proportion of patients reported at least these issues with their family or clinician [13,14]. In a mixed cohort of allogeneic and autologous HCT recipients the absence of ACP was associated with significant reduction in overall survival, but the influence of ACP on EOL care was not described [14]. A more recent study of adult HCT recipients (39% allogeneic) reported that 44% had completed ACP and only 19% used palliative care consultation but did not examine the association of ACP with healthcare utilization at the EOL [15]. To better understand whether ACP may influence EOL healthcare utilization and quality of death in HCT, we evaluated the presence of ACP and explored the association of ACP with intensive healthcare utilization and EOL outcomes in a large modern cohort of deceased adult allogeneic HCT recipients.

## METHODS

We performed a retrospective chart review of adults 18 years and older at time of first allogeneic HCT at Stanford University Hospitals occurring between January 2008 and August 2015. All patients who were subsequently deceased after HCT were included in the study cohort. A comprehensive review of the Stanford electronic medical record (EMR) was used to augment the Stanford University Blood and Marrow Transplant database, which contains extensive information on demographic, disease, and HCT details and HCT outcomes. The Stanford EMR was used to obtain AD documentation, intensive care unit (ICU) days, use of mechanical ventilation, and location of death. An identical data abstraction was performed for study patients who received post-HCT services in the Kaiser Permanente healthcare system (23% of the entire study cohort). AD completion was defined as any document uploaded in the EMR that provided specification about a patient's healthcare power of attorney and EOL wishes. Timing of the AD was defined as documentation pre-HCT, during HCT (day 0 [day of HCT] to day +30), or post-HCT. Each individual AD was reviewed to categorize patient EOL preferences. Our outcomes of interest were healthcare utilization, as defined by ICU stay at any time after HCT, within 30 days of death, and within 14 days of death; use of mechanical ventilation at any time after HCT; and location of death.

Univariate and multivariable logistic regression were performed to explore associations between AD completion and each outcome. We included all variables shown in Table 1 in the multivariable analyses. In addition, in the subset of patients with a documented AD, we explored the association of these same outcomes and the EOL preferences expressed on the AD. All significance testing was assessed at a 2-sided alpha level of .05, and no adjustments were made for multiple comparisons because of the exploratory nature of our analysis. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Study Population and AD Uptake Among HCT Recipients

As shown in the cohort diagram (Figure 1), 1031 consecutive patients underwent allogeneic HCT at Stanford Hospitals between January 2008 and August 2015; 422 were deceased by August 2016 and included in the study analysis.

Forty-four percent had documentation of completed AD before death; of those completing an AD, 77% were documented pretransplant or during the transplant period.

The demographic and clinical characteristics of the study cohort are summarized in Table 1. In unadjusted analyses patients with ADs were significantly older (median 59 years versus 51 years,  $P < .0001$ ) and more likely to undergo reduced-intensity as opposed to myeloablative HCT (51% versus 35%,  $P = .0007$ ). Non-Hispanic whites more frequently completed ADs (51%) relative to Hispanic (22%) and Asian (35%) patients ( $P = .0007$ ). Those who died secondary to primary disease relapse or progression were more likely to complete an AD (48%) than those who died from graft-versus-host disease (41%) or infection (24%;  $P = .04$ ). Twenty-five percent of those dying within the first 100 days of HCT had documented ADs as opposed to 49% who died more than 1 year after HCT ( $P < .001$ ). No significant differences in AD completion were seen based on gender, primary disease, disease status at HCT, year of HCT, donor, and presence or absence of graft-versus-host disease.

### Use of High-Intensity Healthcare Interventions and AD Completion

Patients without AD completion were more likely to use the ICU at any time after HCT (52% versus 41%,  $P = .03$ ), within 30 days of death (40% versus 25%,  $P = .001$ ), and within 2 weeks of death (36% versus 21%,  $P = .001$ ) (Table 2). Similarly, patients without ADs were more likely to experience mechanical ventilation at any time after HCT (37% versus 21%,  $P = .0007$ ). Significant differences were demonstrated in location of death among patients with and without documented ADs: 58% of those without ADs died in the ICU or non-ICU hospital and 22% died in hospice, whereas 46% with an AD died in the ICU or non-ICU hospital and 33% died in hospice. Among patients who completed ADs, 69% had AD documentation stating the wish not to prolong life if terminally ill. Documented wish not to prolong life was significantly associated with less frequent ICU admission (35% versus 64%,  $P = .006$ ) and reduced mechanical ventilation (16% versus 32%,  $P = .007$ ) after HCT when compared with wish to prolong life (Table 3).

### Associations with Death in the ICU

Exploratory analyses found that myeloablative conditioning (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.38 to 3.50) and death within 100 days of HCT (OR, 3.8; 95% CI, 2.19 to 6.75) were significantly associated with increased odds of death in the ICU in univariate analyses, whereas older age (OR, .98; 95% CI, .96 to .99), documented AD (OR, .44; 95% CI, .27 to .72), and death due to primary disease (OR, .1; 95% CI, .05 to .21) or to graft-versus-host disease (OR, .3; 95% CI, .13 to .59) were associated with a lower odds of death in the ICU (Table 4). Only cause of death and timing of death remained significantly associated with death in the ICU in multivariable analysis after adjusting for all relevant baseline variables.

## DISCUSSION

In this large retrospective study of ACP in deceased allogeneic HCT recipients transplanted from 2008 to 2015, we demonstrated that documentation of an AD remains unsatisfactory with healthcare proxy and EOL wishes documented in less than half of the study cohort. We also found that documentation of ADs was associated with reductions in intensive healthcare utilization such as ICU admission and

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