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1. Feasibility and Outcomes of Allogeneic Hematopoietic Cell Transplantation (HCT) Compared to Conventional Therapy for Older and Medically Infirm Patients Diagnosed with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndromes: A Prospective Observational Study

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2.0 INTRODUCTION

The nature of acute myeloid leukemia (AML) changes with age. Different cut-offs have been used to define older AML patients, the most common has been age ≥60 years. When compared with younger adults, AML in patients aged ≥60 years is more frequently preceded by a myelodysplastic syndrome (MDS), has unfavorable cytogenetics, more commonly expresses multidrug resistance, and hence responds less well to chemotherapy [1-3]. In addition, older AML patients are frailer with poor performance status[3] and probably higher comorbidity burden similar to other aging populations [4-6]. As a result, treating aging individuals with AML has been a challenge with only ≤10% patient surviving longer than 5 years.

The advent of nonmyeloablative or reduced-intensity conditioning regimens in the past decade has broadened the eligibility criteria for allogeneic HCT to include older and medically infirm patients. Preliminary data on nonmyeloablative allogeneic HCT among small numbers of older AML patients shows 35-50% survival rates at 3-years, better than expected with conventional chemotherapy [7]. However, extrapolation of these results to the general older AML population is difficult, as they include only those patients who were enrolled onto the HCT protocols. Likewise, patients with a relatively high burden of comorbidities are likely excluded from allogeneic HCT, with this selection bias confounding interpretation of HCT results. The percentages of patients not referred for HCT because of lack of insurance coverage, rapidly progressing disease, poor general condition, or physician preference are unknown.

Our primary goal here is to investigate how often older and medically infirm patients, who are diagnosed with AML or high-risk myelodysplastic syndromes (MDS) and treated with induction therapy, undergo allogeneic HCT in four collaborating institutions. We will investigate different factors that might affect the rate of referral to allogeneic HCT. These rates and reasons will be compared to those in younger and healthier AML/MDS patients. Understanding selection bias, we will follow the prospectively enrolled patients for additional 24 months and describe their outcomes comparing allogeneic HCT versus conventional therapy.

3. BACKGROUND

3.1 AML in older patients:

In 2006, an estimated 13,410 individuals (7,060 men, 6,350 women) in the United States (US) developed AML, while another 8,990 individuals (5,020 men, 3,970 women) died from the disease [8]. AML is a disease of the elderly with a median age at diagnosis of 68 years. While the average annual incidence of AML is approximately 3.43 per 100,000, it increases progressively with age, to a peak of 55.1 per 100,000 at age ≥65 [9]. Moreover, demographic changes in the US population suggest that patients ≥65 years old will constitute 20% at 2030 and they will experience a 77% increase in diagnoses of AML between years 2010 and 2030 [10]. Thus, establishing novel criteria for outcome prediction among older AML patients has become an important future goal.

Research on anti-leukemia therapy and improvements in supportive care in the past three decades has resulted in relative improvement in the outcomes of AML with 5-year survival of about 20%.[9]. Nevertheless, the progress in treating older patients with AML has been very limited [11], with 5-year survival rates of only 5.3% and 1.6% for patients aged 65-74 and ≥75 years compared to 45.5% for those <45 years, respectively [9]. There are many presumed reasons for the poor outcomes among older AML patients. When compared with younger adults, AML in patients aged ≥60 years is thought to be more aggressive given more frequent antecedent blood dyscrasias, more frequent unfavorable cytogenetic abnormalities, more common expression of multi-drug resistance proteins such as P-glycoprotein, and hence poor response to chemotherapy.[1-3]

On the other hand, older AML patients might experience relatively high day-30 NRM (up to 25%[12] compared to 0-10% among younger patients) [3,12]. These results have limited the accrual of older AML patients to clinical trials exploring novel or higher intensity treatments, resulting in sub-optimal therapy of their leukemia. Whether age per se or its interaction with other risk factors is responsible for the high NRM is not really known. For example, poorer performance status was associated with increased mortality among older patients in the Southwest Oncology Group (SWOG) retrospective study [3]. Biological aging is hypothetically composed of three parameters: age, physical function, and organ comorbidities. Indeed, among 427 cancer patients, age, functional impairment, and comorbidities were found to independently predict patient survival regardless of the type of cancer [13]. To date, the role of comorbidities in the decision-making for treatment of older AML patients has not been carefully analyzed.

3.2 Comorbidities and Cancer:

Comorbidities are likely the main factor behind morbidity and mortality after treatment of older patients with cancer. This is in particular since First; in a 'typical' geriatric series, individuals, who are 65 years of age and older suffer on average from three different diseases [4]. Secondly, previous research has demonstrated that severity of a given comorbidity could significantly alter the type of initial anti-cancer treatment. For example, Van Spronsen et al determined that 50% and 15% less chemotherapy were administered to older patients with Hodgkin and non-Hodgkin lymphomas and comorbidities, respectively, when compared to those without comorbidities [14]. In addition, age and comorbidities have been identified as prognostic factors for long-term QOL of cancer patients [15-19]. Comorbidity has an independent impact from functional status and, therefore, could provide additional prognostic information in older cancer patients [20].

Nevertheless, patients with comorbidities have often been excluded from clinical trials, and there has been little information on how to translate results from cooperative studies to given patients with comorbidities. In particular, information on the prevalence of comorbidities among AML patients at diagnosis, particularly those ≥60 years of age is lacking from the literature. Likewise, the impact of different comorbidities on treatment compliance, toxicity, eligibility for HCT, and eventual outcomes of AML patients is unknown.

Certain biomarkers have a track-record of being associated with specific organ comorbidity among the general population of patients and have the potential to influence treatment-related morbidity and mortality. In particular, serum albumin has been seen to inversely correlate with age, smoking, obesity, and hypertension. It serves as a marker of inflammatory status and predicts cardiovascular mortality [21]. High serum ferritin is an acute phase reactant and a suggested measure of iron overload, which has been linked to post-HCT infections, hepatic complications, and pulmonary complications [22-25]. C-reactive protein (CRP) is an acute phase reactant that was found to predict infection, cardiac complications, and mortality [25,26]. Finally, recent reports highlighted the importance of vitamin D levels as a marker of various autoimmune diseases and a predictor of GVHD [27]. We will carefully assess the contribution of these markers to different outcomes after diagnosis of AML. Furthermore, we will evaluate the possible additional prognostic impacts of pulmonary function tests (PFT), particularly diffusion capacity of carbon monoxide (DLco) – after correction of hemoglobin – and the forced expiratory volume in one second (FEV1) on outcomes.

3.3 Allogeneic HCT for older and medically infirm AML patient:

Allogeneic HCT is a potentially curative treatment for many patients with AML. Historically, high-intensity conditioning regimens have been used with the dual aims of disease eradication and host immunosuppression for acceptance of the allografts [28-32]. More than a decade ago, reduced-intensity and

truly nonmyeloablative conditioning regimens have been introduced to reduce toxicities and mortality that can be associated with high-intensity conditioning [33-41]. The new regimens rely in part or entirely on graft-versus-leukemia effects for tumor eradication. Many phase II trials of RIC regimens have been published (reviewed in[42]). These regimens allowed older patients, those who failed preceding high-dose HCT, and those with comorbidities to undergo allogeneic HCT.

In two registry studies, investigators analyzed outcomes of older patients diagnosed with AML or myelodysplastic syndromes (MDS) and treated with various reduced-intensity regimens followed by allogeneic HCT. In a study from the European Group of Blood and Marrow Transplantation [43], 449 patients >60 years old had 4-year NRM of 39% and OS of 27%, which were not statistically significantly different from those of younger patients. In the study from the Center of International Blood and Marrow Transplantation Research (CIBMTR), [44] 376 patients >60 years had 2-year NRM of 34% and OS of 34%. Neither study included information on patients' medical comorbidities.

The Seattle Consortium includes 23 collaborating institutions which have enrolled 372 patients aged ≥60 years into 21 prospective clinical trials investigating allogeneic HCT after nonmyeloablative conditioning regimen of 2 Gy total body irradiation alone or with fludarabine 90 mg/m^2. Overall, the cumulative incidence of NRM and the rate of relapse were 27% and 41%, respectively, leading to OS and DFS of 35% and 32%, respectively. Patients did not statistically significantly differ in these outcomes when stratified by age groups of 60-65, 65-70, or >70 years, while HCT-CI scores predicted increased NRM (**Figure 1**). At 5-years, 67% of living patients were entirely well while 33% continued on immunosuppressive medications for chronic GVHD with a median performance status of 90% for both cohorts. Comorbidities and disease risks for relapse, but not age, were the main predictors for survival. In a risk-stratification model, patients with low relapse risk and no comorbidities had 5-year OS of 69%. We concluded that with the use of nonmyeloablative conditioning, age is no longer a barrier to allogeneic HCT.[45]

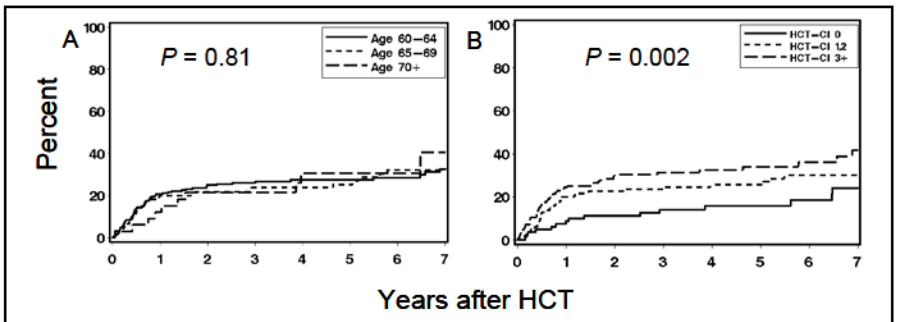

Figure 1: A) Age intervals of 60-64, 65-69, and ≥70 had no impact on NRM (p = 0.81) among recipients of nonmyeloablative allogeneic HCT, while **B)** HCT-CI scores of 0, 1-2, ≥3 were associated with increased NRM (p = 0.002).

While these results suggest tolerance of older AML patients to reduced-intensity allogeneic HCT, it is not clear how to translate these results to the general population of older patients diagnosed with AML. Protocol selection criteria might have been selective for patients with milder comorbidity burden. On the other hand, only 12% of patients treated with HCT between years 2004-2008 were >60 years old, [46] and only 26% of AML patients who were seen in consultation for HCT ended up receiving it. [47] This clearly highlights lack of standard criteria for referral of older AML patients to HCT and lack of information on the feasibility of this approach, which will be addressed in the current protocol.

3.4 Allogeneic HCT versus conventional chemotherapy for older and medically infirm patients:

The role of reduced-intensity HCT in treating older AML patients will remain very limited as long as patients and physicians are reluctant to consider the procedure. A prior SWOG study of this approach was closed early because of poor accrual, and a subsequent study of the Cancer and Leukemia Group B (CALGB) has struggled as well (reviewed in [48]). Both studies were relatively small phase II trials with very modest

accrual goals for a relatively common disease. Thus, there is a reluctance to refer patients for allogeneic HCT. This is likely due to two reasons; first, patients and physicians probably overestimate the benefits of conventional chemotherapy and secondly, many non-transplant physicians likely overestimate the morbidity of the reduced-intensity HCT.

The feasibility of allogeneic HCT was addressed in one relatively small study from the MD Anderson Cancer Center, which included all untreated AML patients aged ≥50 years. Ninety-nine (38%) of a total of 259 enrolled patients achieved CR. Of the 99 patients, 53 were seen by the transplant service for a consult. The reasons for not referring the remaining 46 were unclear in almost half (n=21). Among the 53 patients referred to HCT, suitable HLA-matched donors were found for 26 patients (21 siblings, 5 unrelated) and 14 patients actually underwent HCT (13 from sibling donors). The authors attempted to find one or more chemotherapy pair-mates for each patient who underwent transplantation based on cytogenetic risks, age, and lead time bias. There was a >99% probability that the outcome after RIC was superior to that seen in patients not transplanted. However, the 14 patients who underwent transplantation represent only 26% of those seen by the transplant service, only 14% of all those who achieved CR, and only 5% of the original 259 patients entered into the study. Clearly, this study suffered from small sample size and did not examine the role of comorbidities in the decision not to transplant. We hope to remedy this deficit here. Further, the HCT versus chemotherapy comparison was under-powered, was limited to a single institution, and lacked data on QOL and the patient's decision-making factors. We will carefully address all these points under the current protocol.

QOL is one of the main concerns of older survivors of allogeneic HCT, particularly given the potential late complication such as chronic GVHD. A small study attempted to compare QOL after myeloablative and reduced-intensity allogeneic HCT. All patients were younger than 60 years, [49] which makes the study of limited value to the vast majority of patients treated with reduced-intensity HCT. Investigators observed similar rates of impairment and recovery of QOL 1-year after both HCT modalities. Other small studies assessed the trajectories of QOL impairments after myeloablative HCT and conventional chemotherapy among relatively young patients with contradicting results on which approach resulted in lower QOL [50,51]. To date, no studies have been carried out to assess whether reduced-intensity allogeneic HCT is associated with acceptable QOL among older patients with comorbidities compared to therapy. This information is of great importance for decision-making and will be addressed under **Specific Aim #3**.

3.5 Role of patient preferences, physician perception, and socioeconomic factors in decision-making and outcomes:

Data are limited on patient treatment choices in the setting of AML [52]. We will use a well-accepted single item measure of patients' desired involvement in medical decision making [53]. This measure was previously used to survey 436 newly diagnosed cancer patients and 482 members of the general public. Preferences were elicited using two card sort procedures, each of which described five potential roles in decision making. Findings suggested that the impact of being diagnosed with a life-threatening illness may influence preferences to participate. The majority (59%) of patients wanted physicians to make treatment decisions on their behalf, but 64% of the public thought they would want to select their own treatment if they developed cancer. Socio-demographic variables accounted for only 15% of variance in preferences, suggesting that these variables have limited role in making predictions about patients' decision-making style. The measure had a grade 6 reading level, good face, and content validity, and good reliability with a Cronbach's $\alpha = 0.95$ [54,55].

Both patient and physician measures were recently validated among 43 older patients with advanced AML choosing between induction chemotherapy and non-intensive chemotherapy/best supportive care [52]. In total, 63% of all patients reported not being offered other treatment options despite physician documentation of alternatives. The same study developed a measure assessing estimates of cure and survival. The study showed that patient and physician estimates of cure differed significantly and that regardless of treatment choice, patients reported not being offered treatment options and overestimated their chances of cure.

Socioeconomic status could impact choice of treatment, access to specialized care, and/or survival of cancer patients. Zip code of patient's primary residency has been used to estimate proximity to treatment centers. In general medical practice, proximity to specialized clinical facilities has been shown to influence access to healthcare and outcomes [56]. These findings were also confirmed in the settings of cancer [57,58]. Likewise, distance from centers specialized in HCT seemed to affect survival. Patients from rural areas treated with autologous HCT were found to have an 18% increased relative mortality rate compared to those from urban areas [59]. In allogeneic HCT, driving time to transplant centers was found to independently impact survival. This effect was inversely related to the frequency of clinic visits to the transplantation center [60]. This is not surprising since allogeneic HCT is usually associated with serious complications such as graft-versus-host disease (GVHD) and infection particularly among older and medically infirm patients. Detection and management of these complications would require high level of promptness, a low threshold to intervene, and highly specialized experience [61].

Residential zip codes of patients have also been used to estimate income, where lower income was found to carry poor prognostic risk [62]. However, using zip code to estimate both distance to treatment centers and income would prevent exploring interaction between these two factors. In the current protocol, we will use patients' zip codes to calculate driving time between their primary residence and treatment centers, and then use this information to adjust for the comparisons between patients who were offered versus not offered allogeneic HCT and in the comparison of outcomes between the two treatment groups. Patient-reported income will be collected independently using the study questionnaires.

The health care of an older patient with cancer should include domains beyond the traditional management of cancer. Although evaluation of comorbidities and performance status are critical components, they can be complemented by other domains of geriatric assessment (GA) evaluating physical, cognitive, affective, social, financial, and other factors that could affect the health of an older adult. The National Comprehensive Cancer Network together with the International Society for Geriatric Oncology have recommended the routine use of a GA for patients of $\geq$ 65 years who are diagnosed with cancer [63]. Benefits ranging from prediction of toxicity and survival to assistance in treatment decisions and improving overall well-being of older cancer patients have been proven in non-transplant settings [64-66]. While comorbidities provide data on organ-specific physiologic changes, frailty indices assess the often declining physiologic reserve of multiple systems that is as a feature of aging. Frailty can be manifested by weight loss, weakness, relative immobility, exhaustion, and decrease in physical activity. It can be captured by different tools; one of the most commonly used and proven sensitive for prediction of survival of cancer patients is the Frailty Index [67].

Functional status is a component of GA. It is traditionally assessed by performance status (PS) scales in transplant settings. However, results in geriatric oncology have shown PS scales to underestimate the magnitude of functional impairment in older patients when compared to the more comprehensive assessments provided by use of basic (BADL) and instrumental (IADL) activities of daily living [68,69]. IADL, in particular, was shown to predict OS of older patients with newly diagnosed AML independent from age, PS, or cytogenetics [68,69]. Measurement of gait speed is a simple and objective tool that proves to be very useful for predicting functional

decline, life-expectancy, and mortality after therapy [70]. It was also shown to be as informative as a physical performance battery [71]. Likewise, assessments of cognition, nutrition, psychosocial status, and social support have all been shown to predict treatment tolerance, survival, and ability to comply with treatment instructions.

The prognostic significance of GA has not been adequately tested in the transplant setting. One preliminary small study of 166 patients has shown that GA could uncover additional impairments in health beyond those captured by PS [72]. However, the study collected data on patients aged from 50 years, and only 4 of these were aged ≥70 years. Identifying those components of GA that might add prognostic information to current pre-transplant assessment tools while not adding a substantial burden on patients or transplant teams requires an adequately-sized national study. We will use here the Fried Frailty index to capture frailty among all patients and domains to cover physical, cognitive, psychosocial, and other geriatric problems among patients who are 60 years or older.

3.6 Introducing the use of Comorbidity Indices in Comparative Effectiveness Research of allogeneic HCT:

Until 2004, there has been almost no effort to evaluate the distribution of comorbidities among HCT recipients, to investigate their impacts on HCT outcomes, or to include them in designing clinical trials. We began systematic analyses of the roles of comorbidities on HCT outcomes using a non-transplantation specific comorbidity index, namely the CCI. The study assessed the clinical pretransplant differences between nonmyeloablative and myeloablative recipients of unrelated HCT to determine if the nonmyeloablative regimen truly expanded the HCT options to a new group of patients. To that end, associations between the CCI, as a measure of comorbidities, and other known risk factors with post-HCT NRM and survival were evaluated. Gauging by the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI), nonmyeloablative patients had less (32% versus 69%, $P<0.0001$) overall grade IV (life-threatening) toxicities than myeloablative patients. The lessened cumulative incidences of 1-year (20% versus 32%, $P=1.4$) NRM among nonmyeloablative patients did not reach statistical significance. After adjustment for pretransplant differences, including comorbidity scores, statistically significant lower hazard ratios (HR) for 1-year (0.3, $P=0.04$) NRM were found for nonmyeloablative patients, confirming the importance of a single scoring system for comorbidities. In multivariate analyses of risk factors for outcomes, comorbidities as scored by the CCI, proved to be the only independent factor for predicting overall grade IV toxicity and NRM.

3.7 Development of the HCT-CI:

The CCI was found to have two major limitations among HCT recipients. First, some of the comorbidities described by Charlson were rarely encountered due either to existing exclusion criteria, for example for hepatic comorbidities, or lack of inclusion of laboratory data, for example for pulmonary comorbidities. Second, the CCI did not capture some of the comorbidities that were frequently seen among transplanted patients, such as infections and psychiatric problems. As a result, the CCI identified comorbidities in only 35% of all patients and 12% of recipients of myeloablative HCT (12%) [73].

In order to address these limitations, the CCI was modified in a way that better detected comorbidities among HCT recipients [74]. First, the definitions of several comorbidities were modified by adding progressive impairments of diffusion capacity of carbon monoxide (DLCO) and/or forced expiratory volume in 1-second (FEV1), left ventricular ejection fraction (LVEF) of ≤ 50%, and progressive elevations of levels of bilirubin and hepatic transaminases to the clinical definitions of pulmonary, cardiac, and hepatic comorbidities, respectively. In addition, new cut-offs for serum creatinine levels were set to better define renal comorbidity. Second, all comorbidities encountered in transplanted patients were included in the risk assessment analysis.

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The study included 1055 patients with different hematological diseases who were given allogeneic HCT after nonmyeloablative (n=249) or myeloablative (n=761) conditioning. Two thirds of the patients were randomly assigned to a training set and one third to a validation set. Integer weights of comorbidities were calculated based on adjusted HRs from Cox proportional hazard models of 2-year NRM. The new HCT-CI included 17 comorbidities acquiring scores from 1 to 3.

In the training set, HCT-CI scores of 0, 1, 2, 3, ≥ 4 predicted 2-year NRM of 9%, 14%, 27%, 41%, and 43%, respectively. In the validation set, HCT-CI scores showed higher sensitivity than the CCI scores in capturing comorbidities. HCT-CI scores of 1-2 and ≥ 3 were found in 34% and 28% of patients, while only 10% and 3% of patients had CCI scores of 1 and ≥2, respectively. The HCT-CI scores of 0, 1-2, and ≥3 showed good discrimination of NRM (14%, 21%, and 41%) and survival (71%, 60%, and 34%), respectively (**Figure 2**). The discriminatory capacity of the HCI-CI and CCI, defined as the ability of the model to separate those patients who survived from those who died, were compared using the *c*-statistic or concordance index [75], which was identical to the area under a receiver operating characteristic curve (AUC). A *c*-statistic value of 1.0 indicated perfect predictive discrimination and a value of 0.5 indicated no ability to discriminate. The HCT-CI scores showed higher discriminative power than the CCI scores both for NRM (*c*-statistic of 0.692 versus 0.546, $P < 0.001$) and survival (*c*-statistic of 0.661 versus 0.561, $P < 0.001$). The HCT-CI and a succinct coding tool for comorbidities were added to our study documents. An Editorial accompanying the paper emphasized the importance of this comorbidity scoring system, which might allow refinements of estimates of the outcomes of newly reported research treatments. [76]

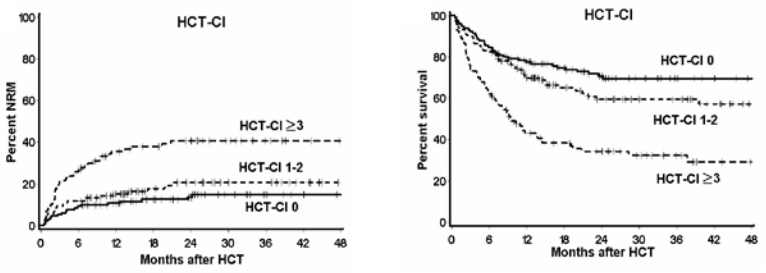

Figure 2: Prediction of NRM and survival by HCT-CI scores among patients of the validation set.

4.0 PROPOSAL

We will investigate in a prospective, longitudinal, observational, multi-institutional study the frequency of receiving allogeneic HCT among patients with AML or MDS considered for induction therapy at multiple institutions. Our primary goal here is to investigate how often older and medically infirm AML patients are referred to undergo allogeneic HCT. We will collect data on outcome-discriminative criteria, such as age, intensity of induction treatment, performance status, cytogenetic risks, and high white blood; in addition to data on patients and physician attitudes towards decision-making style and choice of therapy, socio-demographic variables, and baseline QOL to assess reasons patients may not be offered allogeneic HCT. We will evaluate differences between patients who receive versus those who do not receive allogeneic HCT by comparing the previously mentioned characteristics.

We would like also to understand who benefits from allogeneic HCT and to provide better tools for identifying these patients. Conversely, it is also important to identify patients for whom allogeneic HCT is not recommended because of relatively high treatment-related morbidity and mortality. Other important considerations in these judgments are the toxicity of treatment and the QOL experienced by survivors of either treatment approach. We will observe the two groups of patients who will be treated with allogeneic HCT or conventional therapy over 24 months. Outcome comparisons will be carefully adjusted for differences between patients in comorbidities and outcome-discriminative criteria, socio-demographic factors, decision-making preferences, and baseline QOL scores, which were collected at baseline assessment. These data will help individualize future treatment recommendations.

5.0 OBJECTIVES

5.1 Primary objectives

5.1.1 Feasibility of allogeneic HCT in older and medically infirm patients with AML

5.1.1.1 Estimating the probability of undergoing allogeneic HCT among older and medically infirm AML patients compared to younger and relatively healthier patients.

5.1.1.2 Comparing the characteristics of patients who did versus did not proceed to allogeneic HCT.

5.1.2 Comparison of outcomes among prospectively enrolled older and medically infirm AML patients given allogeneic HCT versus induction therapy

5.1.2.1 Non-relapse mortality (NRM), overall (OS), and disease-free survival (DFS).

5.1.2.2 QOL

5.2 Secondary objectives

5.2.1 Among a subset of patients, studying the impacts of some pulmonary function tests (diffusion capacity of carbon monoxide, and forced expiratory volume in one second) and plasma biomarkers (C-reactive protein, albumin, ferritin, and vitamin D) on:

5.2.1.1 Overall mortality at 8 weeks after induction therapy

5.2.1.2 Feasibility of allogeneic HCT

5.2.1.3 Comparison of outcomes between allogeneic HCT versus conventional therapy

5.3 Tertiary objectives

5.3.1 Preliminary therapy data will be used to develop standardized criteria for the definitions of "intensive" and "less-intensive" treatments. Physicians from around the world will be surveyed about their opinion of the intensity of regimens.

5.3.2 Project results will be disseminated per funding agency's request using novel methods. Methods will include social media, websites, videos, and newsletters. Patients may be asked to appear on video. All methods have the possibility of being published or mentioned in publications.

5.3.3 Among a subset of patients admitted to the ICU at any time point after induction chemotherapy, evaluation of risk factors associated with 90-day and overall survival after ICU admission. Rates of palliative care referrals in patients with and without ICU admissions will be examined.

5.3.4 Comparison of outcomes between patients with secondary AML and patients without secondary AML.

6.0 PATIENT ELIGIBILITY

6.1 Inclusion Criteria

6.1.1 Patients with new diagnoses of non-M3 AML (See study document '2008 WHO Classification of AML') or high-risk MDS, (See study document '2008 WHO Classification and Criteria for MDS') myeloproliferative neoplasms (MPN), or myelofibrosis (MF) (MDS, MPN, or MF showing 10% or more blasts in bone marrow) who:

6.1.1.1 Present for an AML-like treatment that could plausibly produce a complete remission (CR); for example intensive induction chemotherapy, low dose single agent chemotherapy, hypo-methylation agent, or a similar therapy

6.1.1.2 Potentially possible to retrieve follow-up records from the collaborating institution or treating primary care physician.

6.1.2 Patients with primary refractory or first relapse presenting for salvage chemotherapy will be allowed

6.1.3 Patients of $\geq$ 18 years of age and are being treated by the adult AML service.

6.1.4 Able to speak and read English.

6.1.5 Willing and able to provide informed consent.

6.2 Exclusion Criteria

6.2.1 Patients of $\leq$17 years of age or who are $\geq$ 18 and receive treatment under the pediatric AML service.

6.2.2 Patients older than 80 years

6.2.3 Patients with <6 months projected survival due to active second malignancy or other medical problem.

7.0 ENROLLMENT

Typically, AML-specialized physicians at SCCA and collaborating institutions first interact with the patient in a consultation session for a newly diagnosed or relapsed AML or AML-like presentation. During the initial consultation session, physicians explain the diagnosis of AML, risks and benefits of induction therapy versus no treatment. It is common that available clinical trials for induction therapy are presented to the patient during the initial consultation. In such setting it will be appropriate for physicians to approach eligible patients about their potential interest in the observational study. Patients could be approached for study participation by healthcare providers (as part of the consenting conference) or by the protocol research coordinator. To facilitate, this discussion, the physician may use a prepared one-page document explaining the study or leave a prepared one-page letter with the patient that explains the study (See study documents 'Talking Points and Physician-Facilitated Study Letter'). Explanation of the study could be briefed by the physicians and then further explained by the study coordinator for patients treated at the SCCA and by the collaborators' staff at the other sites. Additionally, the study coordinator will be available by phone or email to answer any additional questions raised by patients at any of the collaborating sites.

The study procedures will be outlined and patients will have an opportunity to ask questions. If necessary, discussion about the study may take place by telephone. Signed informed consent is required for enrollment. If the patient is unable to provide written informed consent prior to questionnaire completion because of logistic limitations, questionnaires could be completed on the basis of verbal consent (See study document 'Study Letters and Phone Script for Consenting). However, no research data will be entered into the database until written consent is documented. We expect the need for verbal consent prior to written consent to be rare; priority will be to consent right following a clinic visit. If recruitment cannot be completed in person, priority will go to contacting the patient over the phone, using the phone script. During the consenting process, if the patient indicates they do not want to participate in all aspects of the study, they can mark this on the consent form. Patients that fail to consent to the study will be asked to fill out a consent failure form to understand the reasons behind declining the study. This form will not collect any identifying information and will only record age, gender, race and ethnicity, and main reason for not wanting to consent to the study. We will keep these files in a secure database indefinitely.

Each patient's oncologist will also participate in the study to provide their assessment of the patient's preferences for involvement in treatment decision making, and their estimates of the patient's chances of cure and survival. The oncologists are likely to provide estimates for several of the research participants. For their first assessment, they will be provided with a written explanation of the study. This will be considered their consent document, and by providing information on the assessment, they are consenting to participate in the study. We will not require the physician to provide written consent.

To develop standardized criteria for the definitions of "intensive" and "less-intensive" treatment, we will conduct a survey of renowned experts specializing in the treatment of acute myeloid leukemia (AML). Experts will be approached by email with a link to a brief survey using the Research Electronic Data Capture (REDCap) website (see **Expert Survey**). The survey will include various treatment regimens and the participant is asked to select either "less-intensive", "intensive", or "unsure" for each regimen. Among those regimens chosen as "intensive", the experts will be asked to determine whether regimens are of "high" or "intermediate" intensity. The survey will be done in two (testing and validation) samples of 40-50 experts. We seek 80% agreement rate on each regimen..

8.0 EVALUATION AND END POINTS

The approximate timing for administration of the assessments for this study is detailed in **Table 1** and **Figure 3**. Administration of all assessments will be event-driven but will approximately correspond to the time points illustrated in **Table 1** and **Figure 3**. These time points are recommended dates that could be completed within a limit of 30 days from the proposed time points to take into account suitability of patients' clinical status and reasonable recovery of peripheral blood counts.

Patients who are offered and then treated with HCT will have assessments done at approximately 3, 6, 12, and 18 months after day 0 of HCT. For patients treated with non-HCT treatments (additional conventional therapy or follow up/supportive care), assessments will be done at time points that are roughly corresponding to those who received transplants, which will be at approximately 9, 12, 18, and 24 months from study enrollment. Patients who haven't received further treatment after 6 months from date of study enrollment should follow the time points for assessments for non-HCT treatments. Should these patients later be treated with allogeneic HCT, then dates of assessments will be readjusted to reflect those designed for recipients of HCT (3, 6, 12, and 18 months after day 0 of HCT).

8.1 ASSESSMENTS

8.1.1 Patient-reported socio-demographic variables

8.1.1.1 Race and ethnicity.
8.1.1.2 Age.
8.1.1.3 Gender.
8.1.1.4 Marital status and living situation.
8.1.1.5 Religiosity/spirituality.
8.1.1.6 Work status.
8.1.1.7 Income.
8.1.1.8 Insurance status.
8.1.1.9 Tobacco, alcohol, and recent food intake history.
8.1.1.10 Parenthood.
8.1.1.11 Educational level as classified into five categories: some high school or less, high school graduate, vocational college or some college, college degree, or professional degree [52,77]. Education is especially important in our study since the majority of subjects are outside the labor market.
8.1.1.12 Zip-code of the primary residence. Each zip-code data point will be geocoded using the ArcGIS 9.3 Street-Map North America Postal U.S. address locater (ESRI, Redlands, CA). The location of the treating center will be geocoded into a separate map layer using the U.S. Streets address locater. The ArcGIS Network Analyst extension (ESRI) will be used to calculate driving distance and average driving time along the street network between zip-code of primary residence to the treating center for each patient.

These variables will be assessed once at:
1) Study enrollment.

8.1.2 AML or MDS diagnostic features

8.1.2.1 In peripheral blood and/or bone marrow, information on:
8.1.2.1.1 Morphological diagnosis (See study documents '2008 WHO Classification of AML and 2008 WHO Classification and Criteria for MDS').
8.1.2.1.2 Flow cytometry.
8.1.2.1.3 Cytogenetics and molecular abnormalities:
8.1.2.1.3.1 AML risk-classification (See study document 'AML Risk Status Based on Cytogenetics and Molecular Abnormalities').
8.1.2.1.3.2 MDS features (See study document 'International Prognostic Scoring System for MDS').
8.1.2.1.4 International prognostic scoring system-Revised (IPSS-R) for patients with MDS (See study document 'International Prognostic Scoring System for MDS').

8.1.2.2 In case of extra-medullary disease:
8.1.2.2.1 Flow cytometry of cerebro-spinal fluid.
8.1.2.2.2 Physical examination assessment of any soft tissue mass (chloroma).

8.1.2.2.3 Imaging descriptions of any soft tissue mass (chloroma).

These variables will be assessed once at:

1) Study enrollment.

8.1.3 **PFT, Blood Tests, and Urine Analysis (for patients of FHCRC only)**

8.1.3.1 Pulmonary function tests: particularly, diffusion capacity of carbon monoxide (DLco) after correction for hemoglobin and forced expiratory volume in one second (FEV1).
8.1.3.2 Serum ferritin, albumin, C-reactive protein (CRP), and vitamin D.
8.1.3.3 Urine test: Albumin-creatinine ratio, as well as urine analysis.

These variables will be assessed once at:

1) Study enrollment.

8.1.4 **HCT-CI, comorbidities, and laboratory tests:**

8.1.4.1 Left ventricular ejection fraction, if available or clinically indicated. The closest value (include the date) to the study assessment point. Liver function tests: particularly, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, and albumin. The closest values (include the dates) to the study assessment point.
8.1.4.2 Weight and height and calculation of body mass index. The closest measurements (include the dates) to the study assessment point
8.1.4.3 Laboratory tests, if available or clinically indicated: The closest values (include the dates) to the study assessment point:
- 8.1.4.3.1 Absolute neutrophil count.
- 8.1.4.3.2 Hematocrit percentage.
- 8.1.4.3.3 Platelet count.
- 8.1.4.3.4 Serum creatinine.
- 8.1.4.3.5 Lactate dehydrogenase.
- 8.1.4.3.6 Serum ferritin.
- 8.1.4.3.7 Beta-2 microglobulin.

8.1.4.4 HCT-CI total score and positive comorbidity findings (Please see study documents for HCT-CI and the comorbidity coding tool). If some of the comorbidities included in the HCT-CI were not assessed for a patient, then indicate not available or "NA".
8.1.4.5 Other positive comorbidities, which are not included in the HCT-CI.

These variables will be assessed at:

1) Study enrollment.
2) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.

8.1.5 **Karnofsky performance status (KPS) percentage:**

Please see study document 'The Karnofsky Performance Status Scale' for KPS assessment.

8.1.5.1 As prospectively assessed and documented by clinicians.
8.1.5.2 If not assessed by clinicians at the required study time points: there two options.
8.1.5.3 Request KPS assessment from treating physician.
8.1.5.4 Assignment of KPS by study coordinators at their respective sites after review of medical records.
8.1.5.5 Source of KPS assessment should be noted (clinician versus study coordinator)

KPS will be assessed at:

1) Study enrollment.
2) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.
4) At 9, 12, 18, and 24 months from study enrollment for patient not treated with HCT or at 3, 6, 12, and 18 months after day 0 of allogeneic HCT for recipients of HTC.

8.1.6 **Patient preference surveys:**

8.1.6.1 Patient-reported survey (See study document 'Patient Preference survey) will collect information on:
8.1.6.1.1 Patients' preferred level of involvement in treatment decision-making [53].
8.1.6.1.2 Patients' values regarding length of life vs. QOL.
8.1.6.1.3 Patients' perceptions of the risks and benefits of allogeneic HCT versus other therapies.
8.1.6.1.4 Patients' confidence in their knowledge about allogeneic HCT versus other therapies.
8.1.6.1.5 Patients' estimates of their chances of cure and survival at 1-year.

These variables will be assessed at:

1) Study enrollment.
2) After approximately 1 month from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
4) After approximately 6 months from study enrollment if the patient has not undergone HCT.

8.1.7 **Physician-reported surveys:**

8.1.7.1 8.1.7.1Physician-reported survey (See study documents 'MD Demographics survey and MD Survey') will collect information on:
8.1.7.1.1 Physicians' characteristics.

8.1.7.1.2 Physicians' assessment of their respective patients' preferences for involvement in treatment decision making using Degner's validated tool [53].

8.1.7.1.3 Physicians' estimates of their respective patients' chances of cure and survival at 1-year.

These variables will be assessed at:

1) Study enrollment.
2) After approximately 1 month from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
4) After approximately 6 months from study enrollment if the patient has not undergone HCT.

8.1.8 **Availability of donor:**

We will collect information on:

8.1.8.1 Whether the patient has a potentially available donor.

8.1.8.2 Whether the patient has a definitely available donor.

8.1.8.3 Type of donor: related, unrelated, or cord blood.

8.1.8.4 Degree of HLA-matching: matched, single allele mismatch, one antigen mismatch, HLA-haploidentical, or others.

These variables will be assessed at:

1) Study enrollment.
2) After approximately 1 month from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.

8.1.9 **Treatment details:**

8.1.9.1 Therapy details:

8.1.9.1.1 Clinical trial or not.

8.1.9.1.2 Name of combination therapy.

8.1.9.1.3 Names of each treatment agent.

8.1.9.1.4 Details on doses and duration of each therapy agent.

These variables will be assessed at:

1) All time-points *after* enrollment.

8.1.9.2 Allogeneic HCT:

8.1.9.2.1 Clinical trial or not.

8.1.9.2.2 Type of donor graft received: related, unrelated, or cord blood.

8.1.9.2.3 Degree of HLA-matching of graft received: matched, single allele mismatch, one antigen mismatch, HLA-haploidentical, or others.

8.1.9.2.4 Type of stem cell source: marrow, peripheral blood, or cord blood.
8.1.9.2.5 Type of conditioning regimen: name of agents, doses, and durations.
8.1.9.2.6 CMV serology status of patient and donor.
8.1.9.2.7 Did acute GVHD develop: date, grade, treatments given for acute GVHD?
8.1.9.2.8 Did chronic GVHD develop: date, grade, treatments give for chronic GVHD?
8.1.9.2.9 Did the patient relapse after transplant: if yes, date and details on any treatment given for relapse?
8.1.9.2.10 If the patient received second transplant: same questions about time of transplant.

These variables will be assessed at:

1) After approximately 9, 12, 18, and 24 months after study enrollment or corresponding dates of 3, 6, 12, 18 months after HCT. These dates can be adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.

8.1.10 **AML or MDS response evaluations:**

8.1.10.1 AML or MDs disease status in peripheral blood and/or bone marrow as follows:
8.1.10.1.1 Morphology.
8.1.10.1.2 Flow cytometry.
8.1.10.1.3 Cytogenetics.
8.1.10.1.4 Fluorescence in situ hybridization (FISH).
8.1.10.1.5 Molecular marker abnormalities.

8.1.10.2 In case of extra-medullary disease:
8.1.10.2.1 Flow cytometry of cerebro-spinal fluid.
8.1.10.2.2 Physical examination assessment of any soft tissue mass (chloroma).
8.1.10.2.3 Imaging descriptions of any soft tissue mass (chloroma).

8.1.10.3 Disease responses:
8.1.10.3.1 AML according to the revised recommendations of the International Working Group (IWG) for response criteria and treatment outcomes (please, see study document 'AML Response Criteria').[78]
8.1.10.3.2 MDS according to the modified IWG response criteria (please, see study document 'MDS Response Criteria').[79]

These evaluations will be assessed at:

1) After approximately 1 month from study enrollment and at least 28 days from last therapy cycle.
2) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 6 months from study enrollment and at least 28 days from last therapy cycle.
4) At 3, 6, 12, and 18 months after day 0 of allogeneic HCT for recipients of HC or at 9, 12, 18, and 24 months from study enrolment for patient not treated with HCT.

8.1.11 **Toxicity criteria:**

Toxicity will be graded using and adapted version of the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 (http://ctep.cancer.gov). A copy of the adapted CTCAE v4.0 is available in study document 'Adapted CTC'.
Only toxicities that are graded at III or IV will be documented for this study.

These evaluations will be assessed at:

1) After approximately 1 month from study enrollment and at least 28 days from last therapy cycle.
2) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 6 months from study enrollment and at least 28 days from last therapy cycle.
4) At 3 and 18 months after day 0 of allogeneic HCT for recipients of HTC or at 9 and 24 months from study enrollment for patient not treated with HCT.

8.1.12 **Physical Performance:**

The NIH Toolbox 4-Meter Walk Gait Speed Test will be used to measure locomotion. Gait speed is an indicator of the health of physiological systems. Patients will be asked to walk four meters at their usual pace for one practice session and two timed trials. This test takes three minutes to administer. Study coordinators will meet the patients at regularly scheduled medical appointments and will ask them to complete this quick assessment. For patients with no scheduled appointments within the range of administering the 4-meter walk test, study coordinators will mail a self-administered walk test sheet to be completed by the patient. Previous studies have shown that a self-administered, adapted walk test (the Home-Heart-Walk) had a strong intra-class correlation coefficient (0.98) with a standard walk test.[80,81] The test was well received by participants who had a median age of 64 (range: 49 – 80) years old.[81] The study concluded that self-administered walk test is a reliable and useful method of collecting physical activity data in a medically-challenged, older population.[81] We will implement the same restrictions used in that study by excluding patients with documented heart failure, unstable angina pectoris, fever, complex arrhythmia, resting diastolic blood pressure of 100 mm Hg or more or unstable gait from performing the test on their own.[81]

This test will be given at:

1) Study enrollment.
2) All other time points for collection of patient-reported measures; either performed by study staff at a regularly scheduled medical appointment at study institution or self-administered by patients that do not have a coincidently scheduled medical appointment.

8.1.13 **Outcomes Data:**

8.1.13.1 Alive or deceased.
8.1.13.2 If deceased: cause(s) of death: Root (underlying cause of death), proximate (immediate cause of death), and contributing causes of death.

8.1.13.3 Disease status: remission, relapse, progression, persistent disease supported with by evidence as in (AML response evaluation).

8.1.13.4 For recipients of allogeneic HCT:

8.1.13.4.1 Did acute GVHD develop or not?

8.1.13.4.1.1 If yes: date, grade, organs involved, and treatments given for acute GVHD.

8.1.13.4.2 Current status of acute GVHD: active, resolving, resolved.

8.1.13.4.3 Did chronic GVHD develop or not?

8.1.13.4.3.1 If yes: date, grade, organs involved, and treatments given for chronic GVHD.

8.1.13.5 Current status of chronic GVHD: active, resolving, resolved.

8.1.13.6 Admission to the acute care service within the first 60 days after induction and the first 60 days after consolidation.

8.1.13.7 Admission to the ICU at any time after induction

8.1.13.7.1.1 If yes: dates of admission and discharge from the ICU and hospital, ICU admission diagnosis, most recent AML treatment, and markers of organ failure within 24 hours of ICU admission, including blood counts, blood chemistries, vital signs, and use of life support devices (invasive mechanical ventilation, noninvasive positive pressure ventilation, vasopressors, inotropes, and dialysis). Additionally any positive cultures from 1 week prior to 1 week after ICU admission will be collected.

8.1.13.8 Presence of palliative care referral at any time point after referral to the SCCA.

8.1.14 **Patient-reported QOL measures** (see study document 'Patient Questionnaire Packet**):**

QOL and symptoms will be assessed longitudinally using 8 measures. All QOL questionnaires will be scored according to the recommendations of the developers. We estimate it will take 15 minutes to complete the questionnaires. Please, see study document 'Patient Questionnaire Packet' for the measures of patient-reported QOL.

The Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT, version 4) Scale is a 49-item patient-reported outcome questionnaire that measures QOL in bone marrow transplant patients. The questionnaire includes the standard form of the FACT instrument, namely the FACT-G and a separate BMT scale consisting of 12 items. The BMT scale was enlarged during the validation procedure from 12 to 22 items by McQuellon et al. [82] The FACT-BMT measures physical, functional, social/family and emotional well-being and BMT-specific concerns. All items are rated on a five-point Likert scale. The FACT instrument was recommended by Andrykowski for the investigation of QOL in BMT patients. [83] Patients will be asked to comment on the statements with regard to the time period of the week immediately preceding the specific study time point. To lessen the burden on patients, we will only use the parameters under the standard form of FACT.

The EQ-5D [84] will be used to capture participant-reported utilities that may be used to calculate quality adjusted survival. The EQ-5D contains a five-item survey with three response levels per item measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Conversion tables allow scoring from the 5 items into a summary utility score.

The Social Activity Log (SAL) was designed to capture the frequency and diversity of social activities outside of daily responsibilities. The SAL was adapted by Syrjala et al [85]from one of the few existing measures of social activity participation, the Pleasant Events Schedule. [86]The SAL was developed to focus on activities of survivors with people other than those with whom the survivors live. This was done by reviewing the original content of the Pleasant Events Schedule and identifying items that represented social activities of adults. This content was then reviewed by a focus group of 8 non-cancer adult volunteers who considered their own activities of the previous month and added or revised items. The resulting items were then completed by two sets of volunteers. In that study, the SAL possessed good internal consistency (Cronbach's $\alpha = 0.82$). Internal consistency for non-contact was $\alpha = 0.81$, regular events $\alpha = 0.75$ and special events $\alpha = 0.63$. SF-36 social function and SAL were moderately correlated ($r = .31$) as an evidence of convergent validity.

To further measure social support, we will use the ENRICHD Social Support Instrument (ESSI) [87,88]. This scale was created from items from other validated measures of social support; these items were chosen for their documented predictive validity. Unlike the SAL which measure objective participation in social activities, this measure taps patients' perception of social support, both physical and emotional. The response categories for the seven items range from 1 (none of the time) to 5 (all of the time). Created for use with patients with cardiac disease, it was found to be predictive of death and to have good internal consistency (Cronbach's $\alpha = 0.86$) [79]. The social support measure has also been used in the transplant population but results are not published yet (Syrjala K, Personal Communications).

Depression is a common psychiatric condition during cancer treatment. Most prevalence estimates have ranged between 10 and 25%.[89] Depression could increase symptom burden, [90] affects cognition, [91] QOL, [92] and survival. [74,93,94] We selected the Patient Health Questionnaire-9 (PHQ-9) depression scale as our measure for depression. [95] The PHQ-9 parallels the nine diagnostic symptom criteria of the DSM-IV for Major Depressive Disorder (MDD). The format and temporal framework of the items also correspond to the DSM-IV criteria and can facilitate the follow-up review of symptoms and diagnostic process. With 9-items, participants will rate the frequency of the 9 symptoms over the past 2 weeks on a 4-point Likert scale (0 = not at all, 1 = several days, 2 = more than half of the days, and 3 = nearly every day).[83] The total score of the PHQ-9 ranged from 0 to 27, with higher scores indicating greater severity of depressive symptoms. The internal reliability was reported to be high (Cronbach $\alpha = .91$). Major depressive disorder is diagnosed if 5 or more of the 9 depression symptoms have been present at least "more than half the days" in the past 2 weeks and if one of the symptoms is depressed mood or anhedonia. One of the 9-symptom criteria ("thoughts that you would be better off dead or of hurting yourself in some way") counts as one of the diagnostic criteria for depressive disorders if present at all, regardless of duration. [96] According to the recommendation of Kroenke et al, [96] scores of 0 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 or greater are used to define 5 groups with increasing severity of depressive symptoms. At only 9 items, the PHQ-9 is shorter than most depression screening measures. Unlike most other measures of depression, the PHQ-9 was developed, tested and refined for use with medical patients. This is important because the criterion validity was established in a population with high rates of other physical symptoms and associated non-specific psychological distress. It has also demonstrated acceptability among non-psychiatric patients and among busy primary care providers. [95-97] It is sensitive to change and treatment effects, [98] making it a valid longitudinal clinical tool.

Physical activity as a component of the Fried Frailty Index is measured by a subscale of the Medical Outcomes Study (MOS) Physical Health. The MOS Physical Health Scale measures a broad range of physical functioning, with questions ranging from "Can you bathe and dress yourself?" to "Can you perform vigorous activities, such as running or lifting heavy objects?" Items are rated on a 3-point Likert scale measuring independence in performing the activity. Internal consistency of the physical function score is 0.92.[99]

QOL measures will be assessed at:

1) Study enrollment.
2) After approximately 1 months from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
4) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.
5) At 3, 6, 12, and 18 months after day 0 of allogeneic HCT for recipients of HTC or at 9, 12, 18, and 24 months from study enrollment for patient not treated with HCT.

8.1.15 OARS Multidimensional Functional Assessment Questionnaire (OMFAQ):

Each patient will complete an assessment of his/her respective functional status as a measurement of ability to perform activities of daily living. A portion of the OARS Multidimensional functional Assessment Questionnaire (OMFAQ) will be administered, as it gives a view of the patient's functional status and independence, including: social, economic, mental and physical health, and self-care capacity. The first part includes seven questions regarding the instrumental activities of daily living (commuting, cooking, shopping, and ability to handle finances). The second part includes seven questions regarding the activities of daily living (bathing, dressing, toileting, walking). The scores range from 0 to 2, with lower scores indicating higher levels of dependency on others to complete the activities. The assessment is estimated to take 5 minutes. The OMFAQ will be scored according to the recommendations of the developers. The measures have good validity [100].

These variables will be assessed at:

1) Study enrollment.
2) After approximately 1 months from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
4) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.

5) At 3, 6, 12, and 18 months after day 0 of allogeneic HCT for recipients of HTC or at 9, 12, 18, and 24 months from study enrollment for patient not treated with HCT.

8.1.16 **Satisfaction Surveys:**

The patient will complete two satisfaction surveys: Damian's Satisfaction with Medical Care Scale and Holmes-Rovner's Satisfaction with Treatment Scale[101].
Satisfaction with doctor-patient communication will be assessed with a satisfaction scale published by Damian. Seven items measured on 5 point Likert scale ("completely dissatisfied" to "completely satisfied") and summed to give a total satisfaction score (range 5-35). For example, items include satisfaction with doctor's explanation of the patient's condition, amount of information provided, opportunity to ask questions, honesty, and willingness to discuss patients' fears. This scale detected differences in satisfaction between patients who were or were not provided summary letters of their consultations (32.5 vs. 30, $p = 0.01$).

The Holmes-Rovner's 6 item Satisfaction with Decision Scale will be used to measure satisfaction with treatment choice. The scale is written at an 8^{th} grade level and takes approximately 1 minute to complete. It focuses more on actual satisfaction with decision than O'Connor's decisional conflict scale and is comparable to the Sainfort Post Decision Satisfaction Scale. Since pilot work showed that 48% of 73 transplant patients indicated the highest level of satisfaction with their treatment decisions on the Holmes-Rovner satisfaction scale, results will be dichotomized into maximally satisfied vs. less than maximally satisfied. Regret will be measured at 3 months with two items (wish to change one's mind, and feeling that one would be better off another treatment had been selected) measured on a 6-point Likert scale reflecting frequency of feelings. Cronbach's alpha was 0.80 in a study of 201 men with prostate cancer.

These variables will be assessed at:

1) Study enrollment.
2) After approximately 1 month from study enrollment and at least 28 days from last therapy cycle.
3) After approximately 3 months from study enrollment and at least 28 days from last therapy cycle.
4) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.
5) At 3, 6, 12, and 18 months after day 0 of allogeneic HCT for recipients of HTC or at 9, 12, 18, and 24 months from study enrollment for patient not treated with HCT.

8.1.17 **Frailty**

Frailty will be evaluated according to the five criteria proposed by Fried,[67] following the original cut-off points, with some modifications[102]: 1) Unintentional weight loss (Shrinking) of ≥5% in the last year. 2) Low energy (Exhaustion): Based on two questions asking about interest or pleasure in doing things and asking about feeling down, depressed or hopeless. Those who answered "more than half of the days" or "nearly every day" to at least one of these questions were considered to meet this

criterion. 3) Weakness: The Timed Up and Go is a performance test of physical mobility. The test measures how many seconds it takes an individual to stand up from a standard armchair (approximate seat height of 46 cm), walk a distance of 3 m (10 ft), turn, walk back to the chair, and sit down again. The test was originally reported by Mattias et al., and subsequently modified by Podsiadlo et al.[103] to be a timed test. In a population of frail, community-dwelling older adults, there was good interrater and intrarater reliability (intraclass correlation coefficient = 0.99 for both). The Timed Up and Go score correlated to the scores on the Berg Balance Scale (correlation coefficient [r] = −0.72), gait speed (r = −0.55), and Barthel Index of ADL (r = −0.51) [103]. Guralnik et al.[71] reported gait speed as an important predictor of disability. Duration <7 seconds will meet criteria of frail for weakness. 4) Slowness: Calculated after walking 4 meters, adjusted for sex and height, according to Fried. The cut-off points for 4 meters were established as, in men: height ≤173 cm and time 0.65 m/s; height >1.73 cm and time 0.76 m/s; and for women: height ≤1.59 cm and time 0.65 m/s; and height >1.59 cm and time 0.76 m/s. 5) Low physical activity: will be captured by the MOS Physical Health Scale. Patients scoring in the lowest 20% will be assigned a point for frail for physical activity.

Based on the above five criteria, which incorporates two performance-based measures (timed up-and-go and walk speed over 4 meters) and three self-report measures (exhaustion, weight loss, and physically frail), range of scores will be 0-5; 1-2 indicates pre-frail, 3-5 indicates frail.

FI score will be assessed at:

1) Study enrollment.
2) After approximately 6 months from study enrollment and, if necessary, adjusted within a limit of 30 days to have this assessment done prior to treatment with either allogeneic HCT or additional non-transplant therapies.
3) At 18 months after day 0 of allogeneic HCT for recipients of HTC or 24 months from study enrollment for patient not treated with HCT.
4) If no clinical appointments, the timing can be expanded to within 6 months of the above time points.

8.1.18 Cognition

The Blessed Orientation-Memory-Concentration (BOMC) test consists of six questions designed to screen for cognitive impairment. A score >11 signifies cognitive impairment. The test-retest reliability is high (Spearman rank correlation _ 0.96; P _ 0.001) [104]. The BOMC has excellent validity as a screening instrument, correlates highly with clinicians' ratings of dementia severity (r _ 0.89), predicts results from a longer (26-item) mental status questionnaire, and discriminates between patients with mild, moderate, and severe cognitive deficits [105].
The BOMC has been implemented in the geriatric assessment for older cancer patients in Cooperative Group Clinical Cancer Trials (CALGB).[64] The BOMC has also been recommended by the International Society of Geriatric Oncology for evaluation of cognition in older cancer patients.[106]
Assessment for cognition during study follow up will be allowed within a period of 3 months before or after the corresponding assessment time point in Table 1.

Cognition will be assessed **only in patients 60 years and older** at:

1) Study enrollment.
2) At 6 and 18 months after day 0 of allogeneic HCT for recipients of HTC or at 12 and 24 months from study enrollment for patient not treated with HCT.

8.1.19 **Questions about some geriatric problems only for patients 60 years and older**

The questionnaire will ask the following questions:

8.1.19.1 Vision
8.1.19.2 Hearing
8.1.19.3 Other physical problems or illness
8.1.19.4 Falls

These variables will be assessed once at:

1) Study enrollment

8.1.20 **Recovery Survey:**

The recovery survey will ask the following questions:

8.1.20.1 Marital status
  8.1.20.1.1 Change since diagnosis of AML
  8.1.20.1.2 Current marital status.
8.1.20.2 Work status
  8.1.20.2.1 Change since diagnosis of AML
  8.1.20.2.2 Current work status.
8.1.20.3 Family income
  8.1.20.3.1 Change since diagnosis of AML
  8.1.20.3.2 Current income.

These variables will be assessed once at:

1) 24 months from study enrollment.

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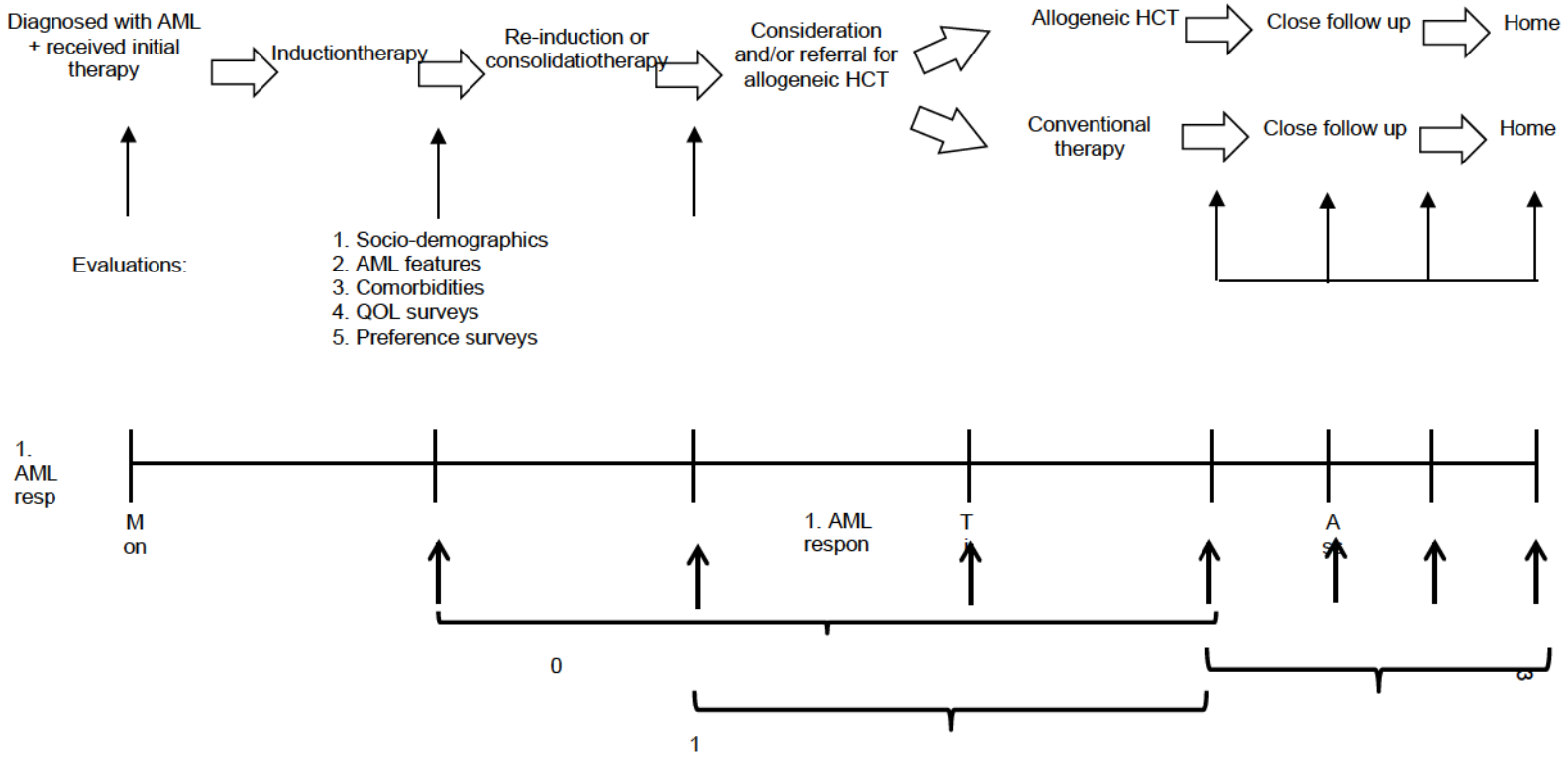
Table 1: Timing of Study Evaluations*

	Timing of assessments							
		Months						
Measures	Enrollment £	1	3	6¥	9¥	12¥	18¥	24¥
Patient-reported socio-demographic & health behaviors survey	X							
AML diagnostic features	X							
HCT-CI, comorbidities, and laboratory tests	X		X	X				X
KPS	X		X	X	X	X	X	X
Physician preference surveys	X	X	X	X**				
Patient Preference Survey	X	X	X	X**				
Availability of donor, and its type	X	X		X				
Treatment details		X	X	X	X	X	X	X
AML response evaluations		X	X	X	X	X	X	X
Toxicity grading		X	X	X	X			X

QOL measures in Questionnaire Packet	X	X	X	X	X	X	X	X
Function measures (Walk Test)	X	X	X	X	X	X	X	X
Timed Up-Go test for FI calculation	X			X				X
Cognition in older patients	X					X		X
Geriatric problems in older patients	X							
Outcomes data		X	X	X	X	X	X	X
PFT, Blood Tests, Urine test (FH site only)	X							
Patient-reported Recovery survey								X

*All dates of assessments are recommended dates that could be adjusted (within a limit of 30 days) to take into account suitability of patients' clinical status and reasonable recovery of peripheral blood counts.
**Assessment will be done if the patient has not undergone HCT
£Assessment should be done after enrollment and preferably before the start of treatment. However, a grace period of one week after the start of treatment is allowed to consent the patient and introduce the assessments. Surveys should be completed by the patients based on their experiences before start of treatment and they should be returned as soon as possible after being completed.
¥If a patient received an allogeneic HCT, then study assessments will be adjusted to reflect the durations of pre-transplant and 3, 6, 12, and 18 months after day 0 of HCT.

Figure 3: Prospective observational study schema



Protocol 2368.00
9.0 STUDY PROCESS

Case Report forms (CRF): CRFs will be collected by the study coordinator at FHCRC and at outside centers. The components of the CRFs should reflect the previously described study evaluations (Table 1).

The CRF will guide the collection of non-patient-reported data into an electronic database through the program REDCap (Research Electronic Data Capture). Though it's not possible to translate a paper CRF directly to an electronic format due to the inherent differences between the two mediums, the translation from paper to computer will stay true to the original format as much as possible. The REDCap platform has an extensive logging feature in order to accommodate audit trails. Every design change, record addition or edit, and data export is automatically logged by user with a date-time stamp. This log is searchable by users with the appropriate user rights through the standard REDCap web-interface. The entire log for a project is exportable to a CSV file at any time by users with the appropriate user rights. REDCap also supports the optional "Data Resolution Workflow" feature, which enables users to open up issues for each variable and each record individually. They can then assign the issue to the appropriate user for resolution. Finally, users have the ability to run a host of standard data quality queries (like missing values, outliers, etc.) in order to check the integrity of the data. Users can also tailor custom data quality queries to check specific criteria relevant for that project. These queries can be run in the same way as the standard data quality queries or in real time at the time of a form submittal by a user.

Data from source documents will be used to transcribe critical protocol data on CRFs. Source documents are documents where patient data are recorded and documented. They include, but are not limited to, clinical summaries, laboratory results, pharmacy dispensing records, and pathology reports. The outside sites will send copies of appropriate source documents to the Coordinating Center (FHCRC) for performance of quality assurance evaluations of the entered data. The original documents will be kept in secured buildings at FHCRC. For each patient, the outside sites will also send a hard copy of the first page of the CRF, which includes the PI's signature verifying each patient's eligibility.

PFT and Biomarker Sample: At enrollment, participants enrolled at FHCRC or Seattle Cancer Care Alliance Southeast Lake Union (SCCA-SELU) will be assessed for DLco and FEV1. If the patient has already been assessed for these tests as part of his/her medical care, this data will be collected from the patient's records. The patient will also be asked to provide a blood sample, either at SCCA-SELU if seen as an outpatient or at UWMC if seen as inpatient, prior to start of initial therapy. Samples will be routed to Research Testing Service (RTS) at UWMC. The patient will also be asked to provide a urine sample to check the albumin-creatinine ratio, as well as urine analysis.

Completion of Surveys: At enrollment, the patient surveys will be administered by the data coordinator in Seattle and collaborating centers' staff at the other sites. Questions raised by patients about the surveys will be answered by the administering staff. Contact information of the Seattle data coordinator will be available for patients enrolled at the outside centers to answer any additional questions about the study or the surveys. All follow-up patient surveys will be collected by the data coordinator located in Seattle. For each completed survey, the patient will receive $20 in remuneration, for a total maximum of $160 over two years.

Collecting/sending surveys: The patient will be asked ahead of time about his/her preferred method of completing the survey: email or pencil-paper (See study document 'Method of Communication'). The web-based questionnaire is preferred but the pencil-paper method will be available per patient preference. The method used for collection of surveys will be recorded for each patient. Through the website, the coordinator

will email the survey at the proposed surveying times and the participant can then fill the survey packet electronically.

Patients who have initially requested the paper-pencil questionnaire will have the questionnaire mailed to their home address with prepaid return-envelopes. Once a completed survey is received, the study coordinator will enter data from the surveys into REDCap. The coordinator will periodically update the survival/death data to ensure the patient is alive prior to initiating the survey reminders.

The study coordinator will contact the patient weekly after sending the survey to encourage completion. At each weekly call (up to one month after sending the survey), the patient will be offered the option to fill out the survey over the phone by answering questions from the study coordinator. The study coordinator will then enter the answers into REDCap. Reasons for inability to complete a survey packet will be collected and recorded. Study staff will carefully review all self-completed paper forms for ambiguous responses and missing data, and clarify these with the participant. The method of survey collection will be recorded.

Physician consent and assessments will be sent to FHCRC physicians either through REDCap, via email, or inter-departmental mail. The same methods will be used by study coordinators at outside centers to collect answers from their respective physicians. Follow up assessments will be handled by FHCRC study coordinators for all physicians, preferably using REDCap communications.

Data Security

Any publication or presentation will summarize patient data and not refer to patients by unique patient number or name to assure patient confidentiality. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are maintained by a designated research coordinator at each institution and kept in a locked room with access restricted to personnel. A study specific database will also use the unique patient number and will not include patient names. Access to the database will be restricted by electronic password protection and restricted access to computers (i.e., locked offices).

REDCap is located on two servers that are protected by a firewall. Each individual that needs to access REDCap (that is, the study coordinators and investigators) has his/her own account. REDCap implements authentication to validate the identity of end-users that log in to the system. Each account can only have access to projects in REDCap that the person has been invited to. The FHCRC Study Coordinator will determine which part of the project other users have access to. REDCap utilizes an auto-logout setting, which is customizable (default auto-logout time is 30 minutes), and will automatically log a user out of the system if he/she has not had any activity (e.g. clicking, typing, moving the mouse) on his/her current web page for the set amount of time. This prevents someone else from accessing the account and project data if a workstation is left without properly logging out or closing the browser window. To help protect and secure the data stored in REDCap's back-end database, the software application employs various methods to protect against malicious users who may attempt to identify and exploit.

Study Participant Committee:

A number of 12 study participants will be invited to join the study stakeholders. Two participant-stakeholders will be selected randomly from each site and will be involved in research discussions. We will use a random number generator (found at www.randomnumbergenerator.com) to select two numbers between 1 and 100 which will coincide with participants' unique study-related ID. We will generate new numbers for each site. These two participants will be contacted via telephone and will be provided with an explanation about the study objectives and role of stakeholders. If the participant declines participation as a stakeholder, we will use the website to select a new number until we have two participant-stakeholders from each site. Our goal is to

represent all five sites, both genders, various age intervals above 60 years old, and variable burdens of comorbidities.

The construction of this committee preferably to be completed within the first year of the study enrollment.

The study participant committee members will be asked to evaluate our methods in translating key results into language that can be communicated to other participations, in order to improve participation and minimize losses to follow-up, and to future patients, to ensure broad dissemination of results.

Completion of Expert Opinion Surveys:
Upon submission of the completed survey, participating physicians will be entered in a drawing to win one of twenty $50.00 Amazon gift cards. Winners will be randomly selected and notified by email.

10.0 ADVERSE EVENTS

Since the proposed studies are not treatment protocols, there will be no risks in addition to those explained to the patients as parts of their treatments for AML.

There is a risk of breach of confidentiality. We have taken all possible measures to avoid this risk. We will explain to patients this risk in the consent form and we will assure them about our methods to protect their confidentiality.

Psychological and social stress might be associated with informing the patients of their comorbidity scores and how these might impact their treatment outcomes. Each patient has a specified family member, guardian, or friend (depending on the age of patient) who provides support for patients during and after the survey. Potential psychological stress includes knowledge of transplant related complications and fear of treatment failure, chronic illness, and potential death. Each treatment center has trained psychologists, psychiatrists, and social workers available for patients and their families.

PFT could carry the risk of the patients developing cough or feeling light-headed or dizzy. It can also cause a feeling of pressure in the chest, belly, or head. These tests are done in clinical facilities and physicians are available to deal with any situation resulting from these tests.

There is a rare risk of bleeding during collection of research samples. It is rare because we will collect these samples only at baseline before the patient has received any chemotherapy that might result in lowering their platelet counts.

Per IRB rules, only related, unexpected, and serious adverse events will be reported to the appropriate IRB, within ten (10) calendar days of becoming aware of the event.

10.1 Reporting Serious and Unexpected Adverse Events (SAE) from Participating Sites

All unanticipated serious adverse events that are considered related to study participation must be reported to the FHCRC Investigator within 72 hours of learning of the event. The immediate telephone report must be followed by a report faxed to the FHCRC Study Coordinator at 206-667-2303. Any follow-up information must be submitted as soon as the relevant information is available.

11.0 STATISTICAL CONSIDERATIONS

11.1 Introduction and sample size

To improve the strength of the findings as well as reporting of these findings, we will follow the recommendations of STROBE Statement (see study document 'STROBE Criteria') which provides guidelines of how to discuss and report study design, analysis, and findings in manuscript writing.

There is no targeted number for enrollment on this study. Instead, we plan to enroll all eligible patients continuously for duration of 36-40 months from study activation. We anticipate enrolling approximately 1000 patients from all sites but we will allow enrollment of more patients if enrollment rates were unexpectedly higher.

Table 2: Power Calculation for Specific Aim #2

Prevalence of risk factor or group	Increment in HCT incidence (HR)
10%	0.17 (1.9)
20%	0.13 (1.7)
30%	0.11 (1.6)
40%	0.10 (1.6)

Based on a preliminary screen of the SCCA records over years 2008-2009, approximately 180, 125, 120, and 75 eligible patients with AML were seen annually at the 4 collaborating institutions, respectively, for an annual total of 500 patients. We anticipate enrollment rate of approximately ~65% resulting in a total of approximately 1000 patients observed over 3 years. Based on a preliminary screen, we anticipate that 50% (n=500) will be ≥60 years of age. Among the remaining 500 younger patients, we would anticipate (based on historical distribution of comorbidity scores among HCT recipients) that approximately 35% (n = 170) will have significant comorbidities (scores of ≥3). This suggests that the combined cohort of older or medically infirm patients eligible for studying the rate of receiving allogeneic HCT will be approximately 670 patients over 3 years. **Table 2** shows an estimate of the minimal increment in incidence of HCT detectable with 80% power at the 2-sided 0.05 level of significance, for varying assumptions about the prevalence of the risk factor. These estimates assume a time-to-event analysis, 25% overall incidence at 2 years post-initial therapy and 25% incidence of death without HCT as a competing risk.

For the comparison study, power calculations are complicated by the time-dependent nature of the treatment groups, as well as by likely non-proportionality in the hazard ratio for HCT. Were these factors not present, the expected 170 patients undergoing HCT compared to 505 who do not undergo HCT, would provide at least 80% power to detect an increase in OS of 13%, at the 2-sided 0.05 level of significance. Because of the large number of unknown assumptions it is nearly impossible to estimate the true power for the actual analysis that will be done, other than that the detectable effect size is likely considerably larger than 13%. Nevertheless, based on previous experience with time-dependent analyses (such as of chronic graft-versus-host disease after HCT),[107] the overall sample size should be sufficient to detect effects of meaningful clinical magnitude.

11.2 The probability and predictive factors for undergoing allogeneic HCT

(1) Based on sample size calculations (see **Sample Size section)**, we anticipate total sample of 1000 patients contributing to this analysis. Patients of ≥60 years will be ~500 while those <60 years will be ~500 patients. Among younger patients: we anticipate 40% (n=170) will have high comorbidity scores. The cohort of combined older or medically infirm patients eligible for studying the rate of receiving allogeneic HCT will be approximately 670 patients.
(2) The rate of undergoing allogeneic HCT will be estimated for the whole observed population, comparing older/medically infirm patients to all other patients.

(3) Data from patients' preferred level of involvement in treatment decision-making will be analyzed by assessing the overall distribution of the most frequent answers among patients who received HCT versus conventional therapy, using chi-squared test. Comparisons of proportion of patients assigning a particular answer as most important will also be done using chi-squared test. The weighted Kappa-statistic will be used to assess the level of agreement or disagreement between the patient's and physician's responses. Marginal Cox model will be used to account for potential correlation between physician and patient preferences.[108]
(4) Differences in QOL scores between baseline and post-treatment assessments for each patient will be tested in an analysis of variance (ANOVA) model.[109]
(5) To identify independent predictive factors for the feasibility of allogeneic HCT, multivariate Cox proportional-hazards regression models will be used, treating HCT as the event of interest and death without HCT as a competing risk. Associations between the potential predictive variables, described under Methods, and the incidence of allogeneic HCT will be evaluated using a backward stepwise approach. Variables that are significantly associated with each outcome event ($P < .05$) will be included as covariate factors in the subsequent comparisons. Time-dependent covariates for multiple post-exposure therapies will be employed using previously described methods.[110] Results will be expressed as HR for each outcome.

11.3 Comparison of outcomes among older and medically infirm AML patients given allogeneic HCT versus conventional therapy

(1) Older and medically infirm patients who were prospectively enrolled for 2-years under **SA2** and who completed initial intensive therapy will then represent a cohort of patients eligible to receive allogeneic HCT or additional conventional therapy (n=670). Based on preliminary screen of databases of collaborating centers, we estimate that approximately 25% of the 670 patients will undergo HCT within the time frame of the study. Patients who do or do not undergo HCT will be compared for NRM, OS, DFS, toxicities, QOL, function, utilization and satisfaction with care. Survivors at 3, 6, and 9 months will be compared for these two outcomes.
(2) Primary Outcomes: (i) Proportional hazards regression models for the sub-distributions of competing risks[111] will be used to evaluate impact of HCT and other factors on time-to-event outcomes (NRM, OS, and DFS). Since HCT may be received well after completion of induction and consolidation therapy, it will be analyzed as a time-dependent covariate,[110]so that the comparison is based on patients who have survived for comparable lengths of time. Similarly, patients who are not newly diagnosed at enrollment will be handled via left truncation – i.e., they will enter the set of patients at risk based on time since diagnosis. This analysis will be adjusted for the risk-stratification model, including comorbidities, disease response, age, and other variables; pre-exposure QOL scores; socio-demographic variables, including driving time to treating centers, income, marital status, and other variables; ranks of patient and physician surveys of decision-making style and treatment values; and the institution where the patient was treated. The evaluation of HCT as a risk factor may be complicated by the likely non-proportionality of hazards. In the short-term interval after HCT the risk of death may increase relative to those alive but not transplanted, then decline due to decreased relapse. We will assess this possibility by allowing the hazard ratio for HCT to vary by time after transplant in a time-dependent manner. All *P* values will be based on likelihood ratio statistics and will be 2-sided. Multivariate *P* values for a variable will reflect adjustment for all other variables in the model. Measures of precision for the HR or risk differences will be provided in form of confidence intervals.

(ii) Landmark analyses for all patients alive at 3, 6, and 9 months post-induction, based on prior history of HCT, will be used to partially compensate for the time-dependent nature of the intervention and early death. A possible approach to describe the effect of HCT on outcome will be to divide the time axis into short intervals (for example, 3-6 months) and to estimate the actual hazard of the event of interest during the interval in 3 different states: not transplanted, early after transplant, late after transplant. This will be based on a simple

exponential assumption: i.e., the number of events in each state divided by the number of person-years at risk in each state. These hazard rates would yield estimates of OS probabilities, which could then be combined to yield estimates of OS probability over longer intervals, for example 1 or 2 years. The usefulness of such estimates would depend on relative stability of the hazard rates as a function of time since initial therapy.

(iii) Given the expected bias in treatment selection and to further enhance our ability of obtaining accurate statistical inferences, we will use propensity scores. Propensity scores will estimate the probability on the basis of all patients and center characteristics that patients would proceed to allogeneic HCT with the use of proportional hazard model to adjust for between-group differences in the previously mentioned characteristics.[112] The magnitude of divergence of propensity scores between the two approaches will allow us to assess the amount of bias in treatment selection. Inverse- probability-weighting based on the propensity score will then be used as a secondary tool to adjust for differences between the two treatment-groups [113]. This approach will be implemented to create balance and it involves weighting each patient who received HCT by the inverse of the probability that he or she would be selected for HCT and weighting each patient who received conventional treatment by the inverse of the probability that he or she would be selected for conventional treatment. We will verify the performance of the propensity model by comparing the distribution of covariates and propensity scores between treatment groups both before and after inverse probability weighting.[114] Adjusted OS curves will be estimated using the inverse-probability-weighting approach of Cole and Hernan.[115] Assessment of benefit of either approach will be done in quintiles of propensity scores.

(iv) Sensitivity analyses will be performed to better understand any statistical disagreement between the models. First, OS curves for comparing both groups will be estimated using a double robust strategy of combining the inverse-probability weighting with the regression-based estimation [116]. Secondly, propensity scores will be used to construct matched samples from both groups to be used for simple matched pair analyses which adjust for confounding variables. Finally, we will use the method of Lin et al [117] to assess whether the observed differences in the rate of death could be due to an unmeasured confounder.

(3) Secondary Outcomes: (i) The relationship between the choice of treatment (HCT *vs.* non-HCT) and QOL, function, utilization, and satisfaction scores will be examined. Intra-patient differences will be used to analyze changes in QOL from baseline to follow-up assessments. Basic analyses will utilize paired t-tests (for changes over time) and two-sample t-tests (for comparison between groups). In order to make full use of the longitudinal data we will also use generalized estimating equations (GEEs) approach,[118] which can accommodate the within patient correlation structure and arbitrary patterns of missing data. Further, the GEEs approach would allow for the population-average interpretation which is an advantage over, for example, generalized linear mixed models approach.

(ii) The previously described statistical approaches will be used to adjust the comparisons between recipients of allogeneic HCT and conventional therapy for the pre-exposure measures of QOL and preference scores.

(iii) We will compare the quality-adjusted outcomes using the Q-TWiST methodology which weights survival time according to clinical status (alive without relapse or toxicity, relapse, and toxicity) [119-122]

(4) Tertiary Outcomes: (i) The risk factors for mortality after ICU admission in patients with AML will be examined. Survival analysis with logistic regression or Cox proportional hazards model will be used, depending on completeness of patient follow-up. Variables in the model will include the AML-comorbidity model score, history of HCT, AML disease status, absolute neutrophil count, use of life support devices, bacteremia, and creatinine. The above risk factors will be evaluated using AUC and c-statistic to inform development of a potential model to predict ICU mortality. **(ii)** The outcomes of patients with secondary AML will be evaluated as compared to patients with primary AML, after adjusting for percent blasts in the peripheral blood, white blood cell count, and performance status at time of presentation.

11.4 Missing Data

This specific aim depends on a high response rate from patients in providing data. The PI together with the SCCA data coordinator will monitor compliance with the self-reported data on a monthly basis and institute corrective measures if the response rate falls below 75%. These may include closer tracking of patients to make sure clinically significant time points are recognized and evaluation of factors associated with no-response in order to identify populations which require greater efforts. Upon receipt of patient-reported data, completion of individual items will be assessed immediately, so that missing data can be requested.

The linear mixed models analysis will be able to accommodate arbitrary patterns of missing data; however, graphical presentations and logistic regression analysis will be performed to understand the missing data mechanism as well as to identify factors associated with incomplete data for survivors. Plots of change in QOL scores from baseline to 90 days, 6 months, 1-year, and 2-year stratified by time of drop-out will be generated separately for each group to determine pattern of missing data. Logistic regression will be used to identify baseline and clinical characteristics associated with missing data. All demographics and baseline characteristics will be included in the logistic model.

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