Cover Page

A feasibility study of "early" allogeneic hematopoietic cell transplantation for relapsed or refractory high-grade myeloid neoplasms

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Study Protocol with Statistical Analysis Plan

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A feasibility study of "early" allogeneic hematopoietic cell transplantation for relapsed or refractory high-grade myeloid neoplasms

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1. INTRODUCTION

Patients with relapsed/refractory (R/R) high-grade myeloid neoplasms remain a very challenging population to treat. Though the goal for patients being treated with curative intent is to undergo allogeneic hematopoietic cell transplant (HCT), many patients never reach this milestone. Chemotherapy alone is highly unlikely to cure R/R patients. The goal of this study is to administer bridge chemotherapy (with GCLAM) and then, before response to chemotherapy is known, to perform "early" allogeneic hematopoietic cell transplantation with a related or unrelated donor. This combination of bridge chemotherapy has been used at other centers in the US and Europe, as described in Section 2: Background, and we propose this study to evaluate the feasibility of this approach at UW/FHCRC. We also plan to follow patient-reported outcomes and resource utilization data for participants.

2. BACKGROUND

2.1 Approach to relapsed/refractory (R/R) myeloid neoplasms at UW/FHCRC

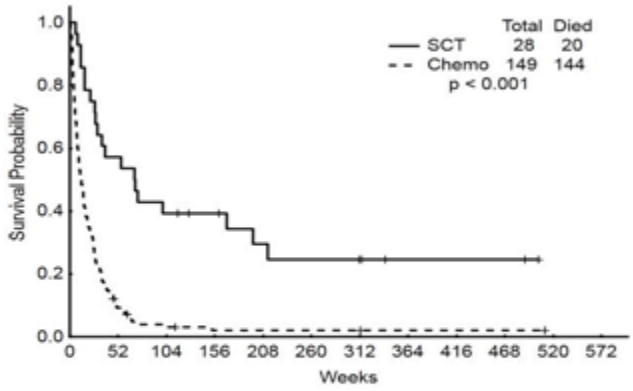
"Resistance" manifested as either failure to enter complete remission (CR) or as relapse from CR is the main cause of death in high-grade myeloid neoplasms, the most common of which is acute myeloid leukemia (AML).[1] The most common approach to resistant AML is use of "salvage" chemotherapy to induce remission defined as a marrow with < 5% blasts either accompanied (CR) or not (CRp/CRi) by blood count recovery and preferably unaccompanied by measurable residual disease (MRD). After remission is achieved, allogeneic HCT is pursued as patients are thought to be otherwise very likely incurable.[2] Allogeneic HCT is used only infrequently as initial therapy of R/R AML. From 2008-2015, 689 UW/FHCRC patients received 1087 induction attempts for R/R AML. Only 73 of the 689 patients received involved initial HCT; that is, only 11% of all patients had allogeneic HCT as their "first salvage" (initial treatment for R/R AML), the time when treatment, including HCT, is presumed mostly likely to be successful. The median OS of this subset was 253 days, and 10% of the 73 patients had documented survival >5 years with multiple other patients still alive without relapse. Ultimately, 227 total R/R AML patients proceeded to undergo HCT as part of their salvage treatment. Thus, a very small proportion of patients with R/R AML proceed directly to HCT rather than receiving salvage chemotherapy. Although it might be supposed that this infrequency reflects lack of suitable donors, data presented below indicate this is not the case.

2.2 Effectiveness of HCT in R/R AML

The relatively infrequent use of HCT as initial therapy of R/R AML contrasts with data suggesting HCT is more effective than chemotherapy in this setting. In 1992 Clift et al. reported that 26 (21%) of 126 patients (median CR duration about 7 months) receiving myeloablative HCT for untreated first relapse of AML were living 2 to 17 years later.[3] This result appears better than seen with use of chemotherapy as initial treatment of first relapse. For example Breems et al. reported a 5-year survival rate of 12% in 270 similar patients (all age < 60 years) whose CR1 duration was 7-18 months.[4] MD Anderson data indicate that, similar to FHCRC, only 10% of patients (n = 285) received HCT as initial treatment for refractory AML. Follow-up data were available for the 149 of the 257 who initially received chemotherapy rather than HCT, with 15 of the 149 subsequently receiving HCT. There was an obvious survival advantage for the HCT approach (see graph below) that persisted after accounting for age, cytogenetics and type of AML (de novo vs. secondary).[5] Another retrospective analysis from MD Anderson attempted to quantify the survival benefit for patients receiving HCT not just limited to primary refractory patients. Unadjusted analysis showed significantly longer survival in patients who underwent HCT in a 396 patient cohort, both in patients who had and hadn't achieved a CR after salvage.[6] Thus, observational data suggest that use of HCT

immediately for R/R AML may lead to better survival than the more standard approach of trying to induce a CR first, then proceeding to HCT.

FIGURE 1: Disparity in overall survival between primary refractory AML patients who receive chemotherapy alone or who receive allogeneic transplantation.



2.3 Feasibility of HCT as therapy of R/R AML

The results described above are likely affected by selection bias since patients who receive HCT as initial therapy for R/R AML may be, in ways that are difficult to quantify, more likely to do well than patients who receive chemotherapy. The only way to eliminate this bias is through randomization between early HCT and the more usual ("late") strategy of HCT once CR after salvage chemotherapy is confirmed. The benefit/risk ratios of early and late HCT approaches seem plausibly similar. In favor of a late approach are data indicating that relapse rates following HCT increase with blast percentage (including MRD), raising the possibility of exposing patients to the mortality/morbidity of HCT despite a substantial probability of later relapse. There is also the belief that leukemia must be reasonably under control to avoid an early relapse before the graft-versus-leukemia effect has time to work, generally thought to be at least 3 months. Conversely, administering chemotherapy and awaiting documentation of complete response before HCT, and if not in remission, giving more chemotherapy, risks development of complications that would reduce the probability of subsequent HCT and, based on the FHCRC data described above has had only a 25% (102/403) chance of producing CR without MRD. It is unknown whether salvage chemotherapy itself contributes to better outcomes, either as a prognostic test identifying patients with truly refractory disease who should not undergo any additional therapy or as a temporizing treatment to reduce disease burden and increase the likelihood of transplant success by giving the graft-versus-leukemia effect time to develop. Only a randomized trial will provide information about the best treatment option: the current approach of salvage chemotherapy, followed by observation of response, then HCT if CR or CRp/CRi vs. the proposed approach of administering re-induction chemotherapy followed by conditioning therapy and "early" allogeneic HCT as soon as possible without awaiting confirmation of CR.

However before embarking on a relatively large randomized study we felt it advisable to gain some confidence that early HCT is feasible at FHCRC. Early HCT will require that donors be identified and

be available quickly once R/R AML had been diagnosed. FHCRC data over a 2 year period indicate that under standard conditions 70 patients already had available donors when they were found to have R/R AML without any additional search requirements, although only 18 of these 70 (26%) received HCT. In addition, the related and unrelated donor search coordinators have developed an "ultra-rapid search" procedure and are confident they can screen related donors and if necessary, identify unrelated donors to allow HCT within 60 days of re-induction chemotherapy. These data suggest that lack of available donors would not be rate limiting in a feasibility study of early HCT. Also affecting feasibility are the possibilities that patients' medical conditions may not allow HCT and the transplant center infrastructure might not be able to accommodate the greater workload accompanying accelerated schedules required for early HCT. Patients, families and physicians might not be willing to proceed to early HCT. The ability to perform early HCT might be increased if re-induction chemotherapy is allowed with the intent to proceed to transplant as early as possible, ideally <60 days after diagnosis, irrespective of the marrow status (CR vs. residual disease vs. refractory disease).

2.4 Experience with early HCT at other centers

Experience of early or "pre-emptive" HCT has come largely from Germany, where chemotherapy has been used as a bridge to allogeneic transplantation. One of the first groups to describe the approach enrolled 103 relapsed/refractory patients with a matched related or unrelated donor available; patients received FLAMSA induction chemotherapy (fludarabine, amsacrine, and cytarabine) from days -12 to -9 followed immediately by a reduced intensity conditioning regimen with 4 Gy total body irradiation day -5, cyclophosphamide on days -4 and -3, and rabbit antithymocyte globulin from days -4 to -2. The complete remission rate was 91.2% and the median OS was 16.4 months, with 32% of patients alive at 4 years of follow-up.[7]

Stölzel et al. investigated this approach, transplanting 95 patients during chemotherapy-induced aplasia.[8] Donors were already identified, and median time from diagnosis to HCT was 36 days (29 days for the 29 patients with sibling donors and 36 days for the 66 patients with unrelated donors.) 30 of the 95 patients had relapsed AML (57% with CR durations < 1 year) and 65 were newly-diagnosed but at "high risk" based on inadequate blast clearance after chemotherapy in 47 patients and/or cytogenetics/molecular features in 18 patients. 52 of the 95 patients received 1 cycle and 43 received 2 cycles of induction/salvage chemotherapy prior to HCT in aplasia: the median marrow blast count was 6% (0-80%) prior to HCT. 71 of the patients received conditioning using fludarabine (30mg/m2 daily day -6 to -2) and melphalan (150mg/m2 day -2). The post-HCT CR rate was 86%. Survival (**FIGURE 2**, panel a) and EFS (Figure 2, panel b) were similar in the 18 high-risk patients in first CR and the 47 primary refractory patients but was also 25-30% in the 30 relapsed patients. Relapse rates appeared relatively low at 100 days and 2 years (Figure 2, panels c and d), as did NRM (Figure 2, panel e at 100 days, panel f at 2 years). AML status at HCT was the principal predictor of outcome (TABLE 1).

FIGURE 2. Stölzel et al[5]. Panels: a) survival; b) event-free survival; c) relapse at 100 days; d) relapse at 2 years; e) non-relapse mortality at 100 days; f) non-relapse mortality at 2 years.

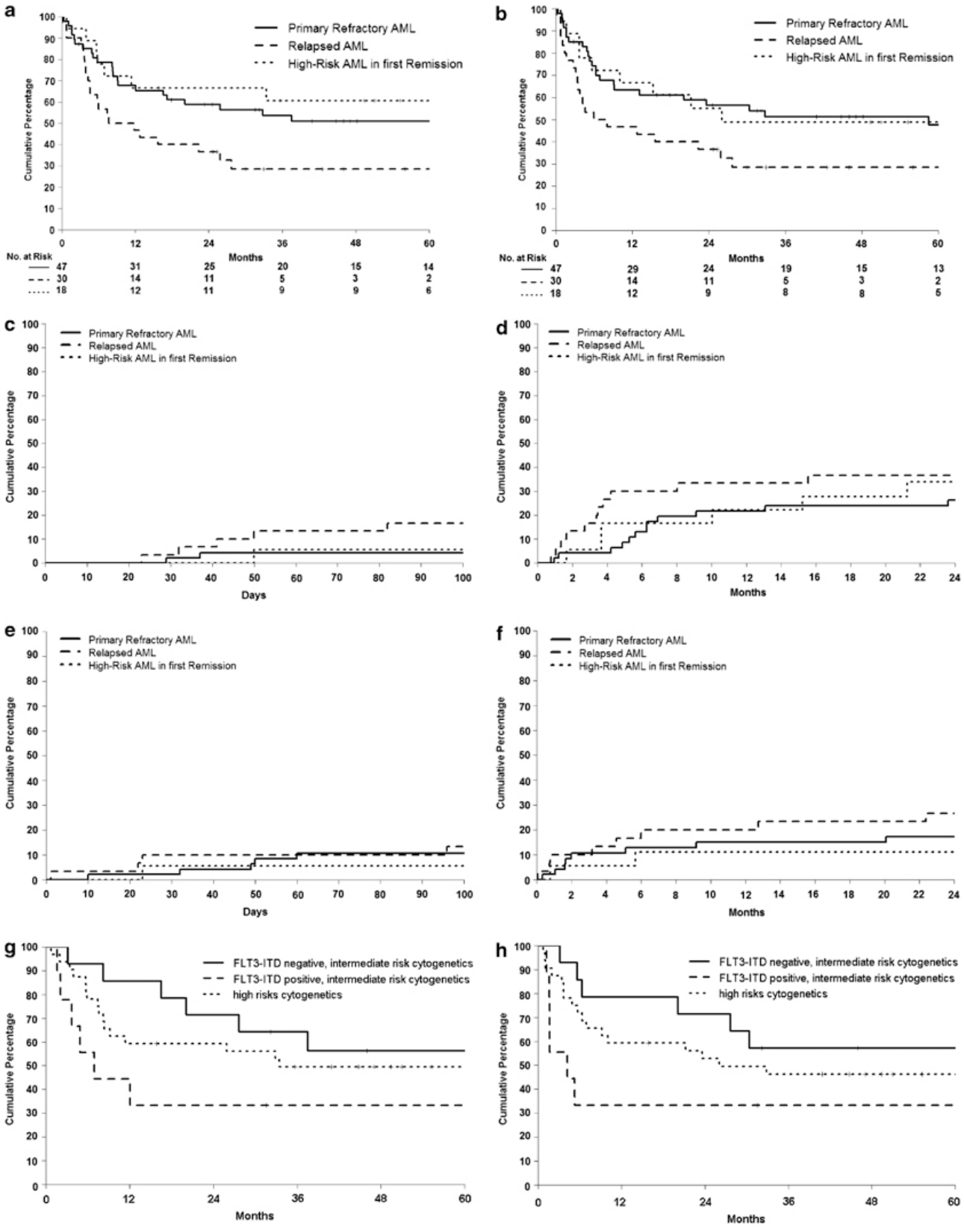


TABLE 1		Event-free Survival		Overall Survival	
	n	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age at HCT (years)					
<40 (reference)	23	1		1	
40–60	52	1.77(0.90–3.48)	0.10	1.82(0.92–3.60)	0.09
>60	20	1.08(0.45–2.62)	0.86	1.11(0.46–2.69)	0.81
AML Status					
Non-Relapsed primary refractory (ref)	47	1		1	
Relapsed	30	1.90(1.05–3.43)	0.085	1.93(1.06-3.51)	0.048
Non-Relapsed other	18	0.98(0.46–2.11)		0.82(0.37-1.82)	
Number of Ara-C cycles					
≤2 (reference)	84	1		1	
>2	11	1.53(0.69–3.39)	0.30	1.59(0.72–3.53)	0.25
Cytogenetic risk					
Standard-risk (reference)	46	1		1	
High-risk	49	1.19.(0.70–2.02)	0.52	1.27(0.74–2.16)	0.39
***FLT3*-ITD mutation status**					
FLT3-ITD negative (reference)	48	1		1	
FLT3-ITD positive	18	1.32(0.63–2.77)	0.46	1.34(0.63–2.81)	0.45
Bone marrow blasts prior to HCT					
<20% (reference)	45	1		1	
≥20%	21	0.71(0.33–1.51)	0.37	0.76(0.36–1.62)	0.48
HCT-CI					
HCT-CI 0 (reference)	30	1		1	
HCT-CI 1–2	43	1.29(0.69–2.41)	0.43	1.24(0.66–2.32)	0.51
HCT-CI >2	22	1.47(0.70–3.08)	0.31	1.56(0.74–3.29)	0.24
Donor type					
Matched related donor (reference)	29	1		1	
Matched unrelated donor	38	1.80(0.92–3.53)	0.09	1.89(0.95–3.76)	0.07
Partially matched unrelated donor	28	1.39(0.67–2.88)	0.38	1.54(0.73–3.27)	0.26

TABLE 1. Univariate analysis demonstrating effects of variables on event-free survival and overall survival as demonstrated by Stölzel et al[8]. The only factor significantly influencing OS is AML status at the time of treatment (p = 0.048); notably other factors, including percentage of BM blasts prior to HCT, did not significantly affect outcomes.

The same authors have recently updated their experience with early HCT in R/R AML by performing a larger multicenter trial with a standardized re-induction and conditioning regimen.[9] They gave clofarabine + ara-C (1 g/m2 daily X 5) to 84 patients, median age 61 (43 relapsed after a median CR1 duration of 6 months, 41 refractory to initial therapy) with the intent of proceeding to HCT as soon as possible, including in aplasia after a day 15 marrow. 26% of the patients had < 5% blasts on day 15. 2/3 of the patients (56/84) received HCT: 53 using blood as stem cell source, 10 with HLA identical donors, 30 with well-matched unrelated donors, and 16 with partially matched unrelated donors. 39 of the 84 had a donor identified prior to enrollment; 32 of these 39 received HCT a median of 29 days after enrollment as did 24 of the 45 without a donor identified at enrollment at a median of 37 days. Conditioning was clofarabine (30mg/m2 days minus 6 to minus 3) + melphalan (140mg/m2 on day minus 2).

With this early approach to HCT, 60% (50/84) attained CR which included CR, CRi, and CR with > 95% donor chimerism. With a median follow-up of 25 months, 2-year probabilities were 52% for survival, 43% for EFS, 26% for relapse, and 23% for NRM. Survival was poorer in patients age > 55 (34%) than for younger patients (67%) but did not appear influenced by whether disease was relapsed or refractory, or by European Leukemia Network (ELN) risk group at enrollment. Likewise EFS was not noted to be affected by donor type or type of CR following HCT but was reported longer in patients with < 5% blasts 15 days after beginning induction chemotherapy (48% vs 31%). By day 100 after HCT 50% of patients had developed acute GVHD, 23% had grade 3-4 acute GVHD; 58% developed chronic GVHD, which was severe in 6%. The reported response and survival rate appear considerably better than might be expected with a standard approach in which HCT is given only after response is established.

In the US, Chen et al reported 30 patients with high-risk clinical features who underwent early (within 4 weeks of reinduction chemotherapy) HCT before count recovery and compared them to 42 patients with standard risk features who only proceeded to HCT more than 4 weeks after chemotherapy and with count recovery.[10] Survival and EFS were similar suggesting that early HCT was no more dangerous or less successful than standard HCT (performed after CR is established), despite the early transplant group having higher risk clinical features. The authors noted that more patients in the high risk group would proceed to potentially curative HCT using their approach.[10]

2.5 Rationale for Study Design at UW/FHCRC

Considerable discussion was held among leukemia and transplant physicians at UW/FHCRC and Roswell Park in the fall of 2015 regarding multiple aspects of the trial, and the consensus decisions and rationale will be described in this next section. The first issue was the study population (see section 3 for eligibility criteria and Table 2 for a description of what prior regimens patients may have received before entering this study). Patients with relapsed AML and refractory AML are the target population, though we will also include patients with high-grade myeloid neoplasms such as MDS-EB2 and CMML in our study population (as long as they had ≥10% blasts at initial diagnosis). Refractory AML patients will have ≥5% abnormal blasts following one cycle of “7+3” or more “intensive” induction chemotherapy, although some do not consider AML refractory unless unresponsive to two cycles of induction. SWOG data indicate that the proportion of patients achieving CR on a 2nd 7+3 (43%) is similar to the proportion doing so following a first course (49%). These data support continuing chemotherapy for patients who do not enter a remission after their first course, rather than stopping treatment due to “refractory disease.” However, these data do not imply patients should receive a second 7+3 if potentially better therapy is available, for example early HCT as intended here. Furthermore, the disparity in CR rates following a first and second courses may be greater with higher intensity regimens [894/1468 (61%) first course, 38/129 (29%) second course, MD Anderson data].[11] Data are insufficient to evaluate differences between CR rates on a first and second GCLAM but the definition of “refractory” AML may depend on intensity of induction regimen. Since patients with relapsed AML or failure to enter a

hematologic CR after the first induction cycle are generally referred for allogeneic HCT, the consensus was to define “refractory” disease as failure to enter remission after one cycle for the purposes of trial eligibility. Please note that patients who meet study eligibility by virtue of this criterion will automatically get a cycle of GCLAM prior to HCT.

We also discussed which relapsed patients would be eligible for the study, since there was concern that multiple courses of GCLAM would increase toxicity and potentially TRM. We were also concerned that in patients with a short duration of CR (< 6 months) following GCLAM , the likelihood of response to GCLAM followed by early HCT was so low as to make the potential risk greater than the potential benefit.[4] Therefore, we chose to exclude patients who had received 2 GCLAM chemotherapy regimens as part of induction, and had a short duration of first CR (<6 months; see inclusion/exclusion criteria below).

We also reached consensus regarding the chemotherapy to be used as a bridge prior to subsequent transplant conditioning regimen. Although allowing physician discretion for AML chemotherapy and HCT conditioning regimen was discussed, it was felt use of only 1 chemotherapy and 1 transplant regimen would facilitate interpretation of the data. The bridge chemotherapy regimen will be GCLAM, a high-dose cytarabine containing regimen which is the most widely used regimen for patients with relapsed/refractory AML at UW/FHCRC. The consensus transplant regimen utilizes fludarabine and melphalan, a so-called “reduced intensity” regimen, because higher intensity regimens were found to be too toxic in other studies. Although recent results from a randomized trial of myeloablative vs. reduced intensity conditioning for AML/MDS found better survival in the group randomized to myeloablative conditioning,[12] patients had to be in a documented remission and presumably were not transplanted early after a reinduction attempt as proposed in this protocol. Additionally, only 20% of patients in the reduced-intensity arm received fludarabine/melphalan, the conditioning regimen specified in the current protocol, with the majority receiving fludarabine/busulfan conditioning. A recent retrospective review suggested that fludarabine/melphalan has a decreased relapse risk compared to fludarabine/busulfan conditioning.[13] We appreciate that some younger patients, particularly those with a low HCT-CI score,[14,15] may not be enrolled in this study or may be taken off study by their treating physicians, who may feel that the risk of relapse following a reduced intensity conditioning approach may be unacceptably high. However, utilizing a reduced intensity regimen may also broaden the pool of potentially eligible patients by allowing older patients to be considered for transplantation and thus balance the decreased enrollment of younger patients. The consensus opinion from FHCRC faculty is that a reduced intensity regimen is necessary to minimize the risk of excess TRM when given soon after AML chemotherapy (see Table 4 below for stopping rule based on TRM for the proposed study).

Additionally, discussion occurred about whether alternative donor transplants (i.e. cord blood or haploidentical donors) should be allowed. For this relatively small feasibility study, we chose to include only patients with a matched related or matched unrelated donor available to keep the population relatively homogeneous and allow standardization of the conditioning regimen across all patients. In the planned larger, randomized trial to follow, we will consider including alternative donor transplants, particularly since the time to donor identification can be quite short for cord blood and haploidentical donors. Notably, a group from the University of Chicago has performed early HCT for a variety of hematologic malignancy primarily used cord blood donors.[16]

Some physicians believed transplant occurring close to 60 days following the start of GCLAM should not be considered “early” transplant. Because of the problems identifying and mobilizing a donor within a shorter time period, we feel that 60 days is a reasonable cut point for this feasibility study, recognizing that the goal of transplantation is closer to 21-30 days. Data from UW/FHCRC showed that among 105 patients who achieved CR after 1st salvage, only about 20% (20 of 105) went to HCT within 2 months (with the remaining 80% going to HCT by 6 months after re-induction). Thus, proceeding to HCT within 60 days would represent considerable acceleration over current practice.

We added a secondary endpoint to evaluate the outcomes of patients who ultimately undergo HCT, but had been taken off study at some point and would therefore count a "failure" for the purposes of this study, because they didn't receive the prescribed conditioning regimen with a pre-specified donor type. However, we will collect information on these patients that will inform treatment plans for any future trial. These patients may include: 1) younger, fit patients who may be taken off study to receive myeloablative conditioning; 2) patients without a matched related or unrelated donor who may undergo an alternative donor transplant; or 3) patients who undergo a transplant outside of the 60-day window dictated by the study.

Due to the fact that several patients were considered "failures" or not able to enroll on the study at all because they only had 9/10 matched donors, we discussed the possibility of adding 9/10 matched donors as another potential donor source if a matched sibling donor or matched unrelated donor is unavailable. The PI had multiple discussions with the transplant team and with the study-specific steering committee about the feasibility and logistics of this change. If immunosuppression is prolonged to decrease the risk of GVHD, outcomes are similar for 9/10 donors.[17-19] Therefore, 9/10 donors will be added to the potential donor sources for patients on this trial.

3. OBJECTIVES

Principal objective

1. To evaluate the feasibility of "early" allogeneic hematopoietic cell transplant (HCT) for patients with relapsed or refractory (R/R) high-grade myeloid neoplasms. The feasibility of this trial is defined in Section 12.1.

Secondary objectives

1. Estimate relapse-free survival (RFS), acute GVHD, TRM, event-free survival (EFS), overall survival (OS), and complete remission (with or without measurable disease) among patients who receive early HCT. Endpoints applicable to patients who don't receive early transplant (survival endpoints and remission) will be also be estimated for all patients enrolled on the study.
2. Assess factors that distinguish patients who receive early HCT from those who do not
3. Demonstrate the feasibility of collecting patient-reported outcomes and resource utilization data for trial participants
4. Describe the outcomes of patients enrolled who went on to allogeneic HCT off-study

Exploratory objectives

1. Compare RFS, EFS, OS, acute GVHD, and TRM between patients in the feasibility study and matched patients who were transplanted with standard scheduling

4. ELIGIBILITY

4.1 Inclusion and exclusion criteria at the time of enrollment

Inclusion criteria (enrollment):

1. Age 18-75 years old (inclusive)
2. Relapsed or refractory high-grade myeloid neoplasms, defined as having a blast count of ≥10% blasts at the time of initial diagnosis. Examples include MDS (EB-2, with ≥10% blasts at initial diagnosis), AML, or chronic myelomonocytic leukemia (CMML-2). Standard definitions of relapse will apply (i.e., characterized by ≥5% abnormal blasts or blast equivalents as assessed by multiparameter flow cytometry or morphologic examination; peripheral blood blasts or blast equivalents; or extramedullary granulocytic sarcoma, per ELN

2017 guidelines). Bone marrow aspirate/biopsy will be accepted if performed outside UW/FHCRC. Determination of disease status should occur within 30 days of signing informed consent.

a. R/R high-grade myeloid neoplasm following intensive induction chemotherapy. **Relapsed high-grade myeloid neoplasm:** Patients will be classified as relapsed if they have ≥5% blasts after being in a CR following treatment for high-grade myeloid neoplasm. **Refractory high-grade myeloid neoplasm:** Patients may be classified as refractory if they have received at least one prior cycle of induction chemotherapy, whether with GCLAM or another regimen.
    i. Patients may have received up to two courses of intensive induction chemotherapy during initial treatment prior to enrollment on this protocol. For example, patients who have received two courses of GCLAM (or similar) chemotherapy, with most recent high-dose cytarabine-containing chemotherapy >6 months ago and CR lasting >6 months, will be eligible for this protocol. Regimens "similar to GCLAM" would include cytarabine at doses of 1g/m^2 for at least 5 doses; examples of regimens "similar to GCLAM" would be GCLA, FLAG, and FLAG-ida. However, patients who received more than two courses of GCLAM (or similar) chemotherapy, or patients who received two courses of GCLAM and had CR lasting <6 months, would not be eligible. See **TABLE 2** for examples of eligible prior treatment by disease status.

b. R/R high-grade myeloid neoplasm following less intensive induction chemotherapy. Patients who have received at least three cycles of treatment with a hypomethylating agent (HMA; such as azacitidine or decitabine) and still have ≥10% blasts will be eligible for the study (they will be considered refractory). Similarly, patients who have received three or more cycles of HMA therapy who have had a response (e.g., achieving CR with <5% blasts), but who then progress using standard definitions of relapse, will also be eligible (they will be considered relapsed).

3. Potentially eligible for reduced intensity conditioning based on known organ function (formal organ function testing may occur after consent)
4. Caregiver capable of providing post-HCT care
5. Written informed consent

<u>Exclusion criteria (enrollment)</u>:

1. Prior allogeneic HCT
2. More than two prior courses of induction chemotherapy
3. Relapse after MRD-negative CR within 3 months of most recent GCLAM chemotherapy
4. Low likelihood of being eligible for reduced intensity conditioning HCT based on known information
    a. Cardiac ejection fraction<40% or symptomatic coronary artery disease or uncontrolled arrhythmia, as assessed by MUGA or TTE within previous 3 months and since the most recent anthracycline exposure
    b. DLCOc <40% or FEV1<50%
    c. Estimated GFR < 40 ml/min
    d. Need for supplemental oxygen
    e. Direct bilirubin or ALT >2 x upper limit of normal, unless these abnormalities are thought to be related to Gilbert's disease or leukemic infiltration of hepatic parenchyma
5. Known HIV positivity
6. Pregnant or nursing (to be confirmed with quantitative HCG testing)
7. Invasive solid tumor within 5 years. Non-melanoma skin cancer or in situ malignancies are allowed.
8. Evidence of serious uncontrolled infection
9. ECOG of 3 or 4

TABLE 2. Sample algorithm to determine eligibility for protocol for R/R high-grade myeloid neoplasm patients who received intensive induction chemotherapy. See Inclusion Criteria for details about other regimens considered similar to GCLAM. We have some institutional data for patients who have received two courses of GCLAM, but essentially no experience giving three consecutive courses of GCLAM, so patients who have received more than two courses prior to enrollment on this protocol are ineligible.

Status of disease	**Induction #1**	**Induction #2**	**Eligible for enrollment on 9567?**
Refractory	GCLAM or similar	GCLAM or similar	No
Refractory	GCLAM or similar	n/a	Yes
Refractory	7+3 or similar	GCLAM or similar	Yes
Refractory	7+3 or similar	7+3 or similar	Yes
Relapsed	GCLAM or similar	GCLAM or similar	Possibly*
Relapsed	7+3 or similar	GCLAM or similar	Yes
Relapsed	7+3 or similar	7+3 or similar	Yes
Relapsed	GCLAM or similar	n/a	Yes
Relapsed	7+3 or similar	n/a	Yes

*A patient may potentially be eligible if they had received two cycles of GCLAM chemotherapy >6 months prior to relapse (see Inclusion Criteria 2ai for details).

4.2 Inclusion and exclusion criteria at the time of transplant

For patients eligible for transplantation, the pre-transplant will be performed per standard practice guidelines, and will include the following inclusion/exclusion criteria at a minimum.

Inclusion criteria (transplant):

1. Identified donor (see DONOR SELECTION below for further details)
    a. Matched related or unrelated (one allele mismatch in HLA-A, B, or C OK) donor according to institutional standards
    b. Unrelated volunteer donor who is mismatched with the recipient (i.e. 9/10 match)
2. Caregiver capable of providing post-HCT care, who will be present once induction therapy with GCLAM begins
3. Written informed consent for transplant
4. Either bone marrow or peripheral blood is allowed

Exclusion criteria (transplant):

1. Donor specific antibodies against donor HLA–DQ or –DP
2. Active bacterial, fungal or viral infections unresponsive to medical therapy
3. Active leukemia in the CNS
4. HIV positive
5. Cardiac ejection fraction<40% or symptomatic coronary artery disease or uncontrolled arrhythmia
6. DLCOc <40% or FEV1<50%
7. Estimated GFR<40 ml/min
8. Need for supplemental oxygen
9. Direct bilirubin or ALT >2 x upper limit of normal, unless these abnormalities are thought to be related to Gilbert's disease or leukemic infiltration of hepatic parenchyma

5. DONOR SELECTION

5.1 Donor evaluation

Donor evaluation will be performed per standard practice guidelines. The donor search will be initiated as soon as the patient's HLA-typing is complete, if a donor has not already been identified prior to enrollment on the protocol. If an appropriate donor is not identified, patients will not be eligible for transplantation on this protocol, though their treating physicians may pursue alternative donor transplantation if appropriate.

Identification of an appropriate donor will follow the general guidelines listed below.

- HLA-matched related or unrelated donor. Donors must be:
  - i) Matched for HLA-A, B, C, DRB1 and DQB1 by high resolution typing
  - ii) ***Only a single allele disparity*** will be allowed for HLA-A, B, or C as defined by high resolution typing

- HLA-mismatched unrelated donor.

Unrelated volunteer donors who are mismatched with the recipient within one of the following limitations will be permitted:

i. Mismatch for one HLA class I antigen with or without an additional mismatch for one HLA-class I allele, but matched for HLA-DRB1 and HLA-DQ, OR
ii. Mismatched for two HLA class I alleles, but matched for HLA-DRB1 and HLA-DQ
iii. HLA class I HLA-A, -B, -C allele matched donors allowing for any one or two DRB1 and/or DQB1 antigen/allele mismatch

HLA-matching must be based on results of high resolution typing at HLA-A, -B, -C, -DRB1, and -DQ. If the patient is homozygous at the mismatch HLA class I locus or II locus, the donor must be heterozygous at that locus and one allele must match the patient (i.e., patient is homozygous A*01:01 and donor is heterozygous A*01:01, A*02:01)

5.2 Expected timeline of chemotherapy and transplant

The minimum time between initiation of bridge chemotherapy and initiation of conditioning for HCT will be 14 days and is anticipated to be closer to 21-30 days. This is based on a median time from initiation of chemotherapy to HCT of 29 days (range 19-74) for both patients with matched sibling and matched unrelated donors in the Middeke et al. study[6]. The donor identification process will begin when a patient is determined to have relapsed.

As soon as potential patients are identified for this protocol, the treating physician or the study staff will contact the Clinical Coordinator's Office to determine the patient's donor status. If a donor has not previously been identified, the Clinical Coordinator's Office will work closely with the treating physician to expedite HLA-typing of the patient (if necessary) and donor search (sibling or unrelated). Patients without a donor identified prior to enrollment on this study will have a rapid search performed to help identify a matched related or matched unrelated donor by an experienced search coordinator at UW/FHCRC. Donor may provide either peripheral blood or bone marrow. Patients without a suitable matched related or unrelated donor identified (8/8 matched at HLA-A, -B, -C, -DRB1) will be taken off study and will count as a "failure" to proceed to early HCT; these patients may be eligible to receive an alternative donor transplant if available to them off-study (note that data will still be collected on these patients who end up proceeding to HCT).

Additionally, to aid in the feasibility, the treating physician or study staff will look into the status of patients' dental evaluations and, in female patients >50, timing of most recent mammogram. These studies, and some of the other pre-transplant work-up listed in section 8.3 (particularly pulmonary

function tests and evaluation of ejection fraction), may be done prior to the patients' formal arrival to the transplant service from the leukemia service.

6. PROTOCOL REGISTRATION

A completed eligibility checklist with source documentation, a signed consent form and a signed HIPAA authorization are required for registration. Patients may be enrolled any time between diagnosis of R/R high-grade myeloid neoplasm and when re-induction chemotherapy is completed, provided that they are receiving GCLAM chemotherapy. For questions, please contact the hematology research coordinators at hemeresearch@seattlecca.org or the protocol PI.

7. TREATMENT PLAN: BRIDGE CHEMOTHERAPY WITH GCLAM

7.1 Bridge chemotherapy

All patients will receive bridge chemotherapy after signing consent, prior to anticipated allogeneic HCT. Patients will receive GCLAM chemotherapy (consisting of G-CSF subcutaneously daily on days 0-5, mitoxantrone hydrochloride IV over 60 minutes on days 1-3, cladribine IV over 2 hours daily on days 1-5, and cytarabine IV over 2 hours daily on days 1-5), as this regimen is our current standard of care for R/R AML patients.[20] When protocol 9567 initially opened for accrual, several patients were concurrently enrolled on the R/R arm of protocol 2734 ("A Phase 1/2 Trial of G-CSF, Cladribine, Cytarabine, and Dose-Escalated Mitoxantrone (G-CLAM) in Adults with Newly Diagnosed or Relapsed/Refractory Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndromes (MDS)"), but this protocol has now closed. The chemotherapy plan for GCLAM is listed in TABLE 3; the dosing of mitoxantrone will be either 10mg/m^2 or 16mg/m^2.[20,21] Patients may have previously received a maximum of two cycles of chemotherapy with GCLAM prior to enrollment on this trial. See **TABLE 2** for examples to help determine eligibility for chemotherapy and participation on this clinical trial. Patients will receive a bone marrow aspirate/biopsy prior to the beginning of HCT conditioning, *though results will not determine whether or not to proceed to transplant.*

The treating physician may also elect to add additional chemotherapy agents to the GCLAM backbone at his/her discretion. Such agents may include a tyrosine kinase inhibitor (such as sorafenib) for patients with FLT3-mutated disease or hypomethylating agents such as decitabine or azacitidine. The treating physician must discuss such potential additions to the GCLAM backbone with the PI and study staff so that the reason for the addition is clear and so that such patients can be clearly noted.

Subjects for whom the treating physician chooses a less intensive therapy than GCLAM at the doses described below will be considered a screen failure on this protocol.

The next section describes the drug information for the drugs used in GCLAM, which will be the re-induction chemotherapy used as a bridge to allogeneic transplant. GCLAM has been administered in different forms (particularly with varying doses of mitoxantrone, as studied in protocol FH2734), but TABLE 3 outlines the sample bridge chemotherapy plan.

TABLE 3: Sample GCLAM bridge chemotherapy plan. G-CSF dosing dependent on patient weight (300 μg dose for patients <76kg and 480 μg dose for patients ≥76kg). Day 0 and Day 1 doses of G-CSF may be omitted if WBC>20,000/μl. Day 0 through day 5 of G-CSF may be omitted at the discretion of the treating physician and in consultation with the principal investigator (e.g. to avoid additional pain for patients with existing bone pain. In the case of significant bone pain related to relapsed/refractory high-grade myeloid neoplasm, consideration may be given to omitting G-CSF doses until the bone pain is under control. Once bone pain is controlled, the remaining doses of G-

CSF should be delivered per the chemotherapy schedule pending discussion). Infusion times are approximate. The dosing will be performed using actual body weight.[22]

Day #	Agent	Management plan
0	G-CSF	G-CSF 300 or 480 μg subcutaneous
1	G-CSF Cladribine Cytarabine Mitoxantrone	G-CSF 300 or 480 μg subcutaneous Cladribine 5 mg/m^2 IV over 2 hours Cytarabine 2 g/m^2 IV over 2 hours Mitoxantrone 10 or 16mg/m^2 IV over 60 minutes
2	G-CSF Cladribine Cytarabine Mitoxantrone	G-CSF 300 or 480 μg subcutaneous Cladribine 5 mg/m^2 IV over 2 hours Cytarabine 2 g/m^2 IV over 2 hours Mitoxantrone 10 or 16mg/m^2 IV over 60 minutes
3	G-CSF Cladribine Cytarabine Mitoxantrone	G-CSF 300 or 480 μg subcutaneous Cladribine 5 mg/m^2 IV over 2 hours Cytarabine 2 g/m^2 IV over 2 hours Mitoxantrone 10 or 16mg/m^2 IV over 60 minutes
4	G-CSF Cladribine Cytarabine	G-CSF 300 or 480 μg subcutaneous Cladribine 5 mg/m^2 IV over 2 hours Cytarabine 2 g/m^2 IV over 2 hours
5	G-CSF Cladribine Cytarabine	G-CSF 300 or 480 μg subcutaneous Cladribine 5 mg/m^2 IV over 2 hours Cytarabine 2 g/m^2 IV over 2 hours

7.2 Drug Information on G-CSF (Granulocyte colony-stimulating factor)

Mechanism of Action: G-CSF is a growth factor that stimulates the production, maturation, and activation of neutrophils. Further, it promotes premature release of neutrophils from the bone marrow and enhances their phagocytic capacity.

Pharmacokinetics: Peak G-CSF concentrations after sub-cutaneous dosing occur in 2 to 8 hours, though the onset of action is approximately 24 hours, with plateau concentrations in 3-5 days, and elimination over an 11-20 day period. G-CSF is cleared by systemic degradation. Notably, as G-CSF binds neutrophils, plasma levels are controlled in large part by the absolute neutrophil count.

Adverse Effects (AEs): Common drug-related AEs (occurring in >10% of patients) include fever, petechiae, elevated uric acid, splenomegaly, bone pain, and epistaxis. *Less common drug-related AEs (occurring in 1% -10% of patients)* include hyper- or hypotension, arrhythmias, headache, nausea, vomiting, leukocytosis, and transfusion reaction. *Infrequent drug-related AEs (occurring in <1% of patients)* include acute respiratory distress syndrome, allergic reactions, alopecia, alveolar hemorrhage, arthralgia, bone density decrease, capillary leak syndrome, cerebral hemorrhage, vasculitis, dyspnea, edema, erythema nodosum, hematuria, hemoptysis, hepatomegaly, hypersensitivity, injection site reaction, pericarditis, proteinuria, psoriasis exacerbation, pulmonary infiltrates, renal insufficiency, sickle cell crisis, splenic rupture, Sweet's syndrome, tachycardia, and thrombophlebitis.

Recommended dose adjustments for organ dysfunction: There is limited or no data examining the toxicity of G-CSF in patients with renal or liver dysfunction. Therefore, administration of G-CSF to patients with liver or kidney disease must be done with caution.

7.3 Drug Information on Cladribine (2-chloro-2'-deoxyadenosine, 2-CdA)

Mechanism of Action: Cladribine is a prodrug that is converted to an adenosine deaminase-resistant triphosphate derivative (2-CdATP). This molecule is then activated by deoxycytidine kinase to a 5'-triphosphate derivative (2-CdAMP), which is incorporated into DNA where it acts as a transcription regulator. In addition to its cytotoxic properties in dividing cells, cladribine induces death in quiescent cells of lymphoid origin through an unknown mechanism.

Pharmacokinetics: Cladribine is renally excreted, with 18-35% as unchanged drug. It is able to penetrate the CSF, where it achieves 25% of plasma concentrations. It is 20% protein-bound. The half-life for elimination after a 2-hour infusion is 6.7±2.5 hours in patients with normal renal function.

Adverse Effects: *Common adverse effects (occurring in >10% of patients)* include fever, fatigue, headache, rash, nausea, anorexia, vomiting, myelosuppression (including grade 3/4 neutropenia/thrombocytopenia), injection site reaction, and infection. *Less common adverse effects (occurring in 1 to 10% of patients)* include edema, tachycardia, thrombosis, chills, dizziness, insomnia, malaise, diarrhea or constipation, weakness, myalgias and arthralgias, cough, dyspnea, epistaxis, and diaphoresis. *Rare adverse effects (occurring in <1% of patients)* include aplastic anemia, bacteremia, opportunistic infections, lymphocytopenia, altered mental status, hemolytic anemia, hypersensitivity, myelodysplastic syndrome, quadriparesis, and renal dysfunction/failure.

Reconstitution: Cladribine is supplied as a sterile, preservative-free, isotonic solution containing 10 mg of cladribine (1 mg/mL) in 10 mL single-use vials. Cladribine should be passed through a sterile 0.22µm filter prior to introduction into the infusion bag containing 0.9% Sodium Chloride Injection, USP.

Administration and Compatibility: The use of 5% dextrose is not recommended as a diluent because of increased degradation of cladribine. The infusion solution is stable for 24 hours at room temperature.

Storage and Stability: Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

Recommended Dose Adjustments for Organ Dysfunction: Specific guidelines for cladribine dosing in patients with hepatic/renal dysfunction or hypoalbuminemia are not clearly defined. Because of the potential for compensatory elimination of cladribine in patients with hepatic and/or renal dysfunction, specific guidelines for dosing are difficult to define. Thus, when deciding whether to adjust cladribine doses for renal dysfunction, the risks for potential toxicities (e.g., myelosuppression, neurotoxicity) against the benefits and goals of treatment must be considered.

7.4 Drug Information on Cytarabine (Cytosine arabinoside)

Mechanism of Action: Cytarabine is a synthetic pyrimidine analog, in which the sugar moiety (normally a ribose or deoxyribose) has been replaced with arabinose. Although its mechanism of action is not completely understood, the active form of cytarabine is probably incorporated into the DNA and interferes with DNA synthesis. As such, cytarabine has been found to primarily effect dividing cells, blocking their progression from G_1 to S phase.

Pharmacokinetics: Cytarabine is metabolized by deoxycytidine kinase and other kinases into its most active form (aracytidine triphosphate). Aracytidine triphosphate is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. This balance between the levels of kinases and deaminases is critical for regulating the sensitivity/resistance of cells to the drug. The plasma clearance of cytarabine is biphasic, with an initial rapid phase and more prolonged second clearance phase. The rapid clearance phase has a relatively short half-life ($t_{1/2\alpha}$ = 10 minutes), while the half- life of the second clearance phase is slightly longer ($t_{1/2\beta}$ = 1 – 3 hours). The

nontoxic metabolites from the drug are excreted in the urine, and within 24 hours after the infusion, approximately 80% of these nontoxic metabolites can be recovered from the urine.

Adverse Effects: The dose-limiting toxicity for cytarabine is myelosuppression. *Adverse Events Associated with Standard Dose Cytarabine: Frequent AEs (not definitely quantified)* include the following: myelosuppression (leucopenia, anemia, neutropenia, thrombocytopenia), pyrexia, rash, anorexia, diarrhea, nausea, vomiting, mucositis, anal inflammation or ulceration, hepatic dysfunction or increased liver enzymes, and local thrombophlebitis. *Less frequent AEs (not definitely quantified)* include chest pain, pericarditis, dyspnea dizziness, headache, neural toxicity, neuritis, alopecia, pruritus, skin freckling, skin ulceration, urticaria, abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat, urinary retention, jaundice/hyperbilirubinemia, local site cellulites, renal dysfunction, allergic edema or anaphylaxis, sepsis, and sudden respiratory distress syndrome. *Infrequent AEs (not definitely quantified)* include aseptic meningitis, cardiopulmonary arrest, cerebral dysfunction, cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia), exanthematous pustulosis, hyperuricemia, intestinal pneumonitis, increased lipase, paralysis with intrathecal and IV combination therapy, rhabdomyolysis, veno-occlusive disorder, and death. *Adverse Events Associated with High Dose Cytarabine* include cardiomegaly and cardiomyopathy, coma, severe neurotoxicity, personality change, somnolence, total body alopecia, severe rash or skin desquamation, gastrointestinal ulceration, peritonitis, intestinal pneumatosis, necrotizing colitis, liver abscess or damage, peripheral neuropathy, corneal toxicity, hemorrhagic conjunctivitis, pulmonary edema, sudden respiratory distress syndrome, and sepsis.

Reconstitution: Cytarabine should be reconstituted in sterile water and can be further diluted using either 5% dextrose or sodium chloride solutions into appropriate concentrations for infusion.

Administration and Compatibility: The diluted cytarabine solution should be inspected for particulate matter, discoloration, and haze prior to infusion. If there is evidence of particulate matter, discoloration, or haze the solution should not be infused. Patients should be medicated with standard anti-emetic therapy. Cytarabine is not compatible (1) during Y-site administration with allopurinol, amphotericin B, ganciclovir; (2) in syringe with metoclopropamide; or (3) admixed with fluorouracil, heparin, insulin (regular), nafcillin, oxacillin, penicillin G. Cytarabine may have variable compatibility when admixed with gentamycin, hydrocortisone, and methylpredinsone.

Storage and Stability: Vials of non-reconstituted cytarabine should be stored at room temperature 15°C - 30°C (59°F - 86°F). The diluted cytarabine solution may be stable for up to 48 hours if stored at room temperature.

Drug-Drug Interaction: Reversible decreases in the plasma steady-state concentration for digoxin and cardiac glycosides may occur. Cytarabine may diminish the therapeutic effect of flucytosine. There is *ex vivo* data suggesting that cytarabine may reduce the effectiveness gentamycin for killing *K. pneumoniae*.

Warnings and Precautions: *Ex vivo* and *in vivo* studies have found that cytarabine causes extensive chromosomal damage and potential malignant transformation. Although there have been some case reports describing cytarabine use in pregnant humans, these cases reports are few. Thus, cytarabine is considered Pregnancy Category D. Women should be advised not to become pregnant while receiving cytarabine, and men should be advised not to father a child while receiving cytarabine and for at least 3 months after completing the therapy. It is not known whether cytarabine or its metabolites are excreted in breast milk; thus, it is not recommended for lactating females who are breast-feeding. As with any highly immunosuppressive medication, cytarabine may diminish the effectiveness of dead and live vaccines and enhance the toxic/adverse effect of live vaccines. One should avoid use of live vaccines while receiving it. A small percentage of patients will have a hypersensitivity reaction to cytarabine, and these individuals should not receive the drug again.

Recommended Dose Adjustments for Organ Dysfunction: Guidelines for adjusting cytarabine dose due to renal or liver dysfunction are not standardized, but many clinicians will adjust the dose based upon the function of these organs.

7.5 Drug Information on Mitoxantrone

Mechanism of Action: Mitoxantrone (dihydroxyanthracenedione) is an anthracenedione derivative that intercalates with DNA, resulting in inhibition of nucleic acid synthesis.

Pharmacokinetics: Mitoxantrone is 78% bound to plasma proteins. A three-compartment model was described after a single intravenous dose of mitoxantrone. The mean alpha half-life is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours, and the mean terminal (gamma) or elimination half-life is 23 to 215 hours (median 75 hours). Mitoxantrone has extensive distribution into body tissues and is metabolized in the liver to two main inactive metabolites (monocarboxylic acid derivative and dicarboxylic acid derivative). The major route of excretion for mitoxantrone appears to be biliary into the feces; approximately 11% of the dose is recovered in the urine within 5 days of drug administration, with 65% of this being unchanged drug.

Adverse Effects: *Common adverse effects (occurring in >10% of patients)* include edema, fever, fatigue, headache, alopecia, nausea/vomiting, diarrhea, mucositis/stomatitis, myelosuppression, weakness, dyspnea, cough, and infection. *Less common adverse effects (occurring in 1 to 10% of patients)* include congestive heart failure, decreased left ventricular ejection fraction (LVEF), hypertension, chills, anxiety, cutaneous mycosis, hypocalcemia, hypokalemia, hyponatremia, menorrhagia, jaundice, myalgia, arthralgia, renal failure, proteinuria, rhinitis, diaphoresis, and infection.

Mitoxantrone may cause cardiac toxicity with prolonged administration and doses exceeding 80 to 100 mg/m^2; Appendix D provides an overview of the cardiotoxicity index of individual anthracyclines as well as mitoxantrone. When used after doxorubicin, cardiotoxicity is more frequent; an analysis by the Southwest Oncology Group revealed a risk of 6% at 134 mg/m^2 prior doxorubicin and 60 mg/m^2 mitoxantrone, rising to a 15% risk at 120 mg/m^2 mitoxantrone. Cardiac events reported included arrhythmias, decreased left ventricular function, chronic heart failure, tachycardia, ECG changes, and, infrequently, myocardial infarction. Bradycardia has been rarely reported. Patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease may have more frequent occurrences of cardiac toxicity.

Reconstitution: Mitoxantrone must be diluted prior to use. The dose of mitoxantrone should be to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). Mitoxantrone may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately.

Administration and Compatibility: Care in the administration of mitoxantrone will reduce the chance of extravasation. Mitoxantrone should be administered into the tubing of a freely running intravenous infusion of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes, or eyes. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritus, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein.

Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form.

Storage and Stability: Mitoxantrone should be stored between 15°C - 25°C (59°F - 77°F).

8. TREATMENT PLAN: CONDITIONING AND ALLOGENEIC TRANSPLANT

Once patients have completed GCLAM conditioning, it is expected that they will move on to allogeneic HCT with a suitable related or unrelated donor. Patients will receive a bone marrow

aspirate/biopsy prior to the beginning of HCT conditioning, *though results will not determine whether or not to proceed to transplant.* The details of the allogeneic HCT are described below.

8.1 Donor identification

This topic is discussed in section 5.

8.2 Separate HCT consent

Because many patients will not have an identified donor nor have been formally evaluated for transplant eligibility and attained insurance approval for transplantation when they enroll in this study, they will need to sign a separate consent for transplantation. Participants will undergo standard transplant consultation, medical evaluation and financial clearance. If a donor is identified and the patient's medical condition is appropriate for transplantation, they will sign a separate consent for transplantation. Note that if donor availability or patient medical condition necessitates a different transplant approach, the treating physician may elect to pursue the alternative treatment.

8.3 Pre-transplant evaluation

Patients who have received bridge chemotherapy with GCLAM will be assessed for the eligibility criteria for allogeneic transplant described above, and will sign the separate transplant consent. For patients who are candidates for allogeneic transplant, they will undergo pre-transplant evaluation per standard practice, to include but not limited to:

1) Comprehensive History and Physical Examination including full details of the patient's diagnosis, prior treatment and response, and Karnofsky score (> 16 years)
2) Two view chest x-ray (PA and lateral).
3) EKG
4) MUGA or ECHO for EF evaluation.
5) Baseline pulmonary function studies, (or for pediatric patients, unable to perform pulmonary function tests, then O2 saturation on room air).
6) Lumbar Puncture and CSF analysis for high risk patients per standard practice.
7) Nutritional assessment including height, weight and body surface area
8) Bone marrow aspiration for pathology, flow cytometry, cytogenetic and research studies, within 30 days of planned donor cell infusion
9) CBC with differential and reticulocyte count
10) Serum chemistries including: electrolytes, creatinine, glucose, Ca, Mg, Phos, BUN, uric acid, total protein, total bilirubin and direct/indirect fractions, LDH, AST, ALT, GGT, alk phos, albumin, fasting triglyceride and cholesterol levels
11) ABO and Rh typing and direct Coombs
12) HSV, CMV, VZV and HIV serologies
13) Infectious hepatitis panel
14) Urinalysis
15) HCG (quantitative pregnancy)[PG] (must be obtained on every female patient who is past menarche and pre-menopause
16) Confirmatory HLA typing of recipient and donor

8.4 Treatment plan for conditioning and allogeneic HCT

8.4.1 Donors

Collection of hematopoietic stem cells for unrelated donors: HCT scheduling and collection is arranged through unrelated donor registries. The schedule of G-CSF administration and collection of PBSC is determined as per NMDP or NMDP Cooperative Registry protocol. The physician responsible for HSC collection will obtain informed consent from the donor.

Collection of hematopoietic stem cells for related donors:

TABLE 4: Typical mobilization for Matched Related Donors

Day #	Agent	Management plan
-5	G-CSF	16 µg/kg subcutaneously
-4	G-CSF	16 µg/kg subcutaneously
-3	G-CSF	16 µg/kg subcutaneously
-2	G-CSF	16 µg/kg subcutaneously
-1	G-CSF	16 µg/kg subcutaneously Collection of PBSC*
0		If collection on Day -1 contains less than $5.0x10^6$ CD34+ cells per kg of recipient weight, another PBSC collection will occur

*PBSCs will be collected in the afternoon of day -1, stored at 4ºC overnight, and infused as soon as possible on day 0.

8.4.2 Treatment options for conditioning and immunosuppression options for recipients
Recipients will receive one of two different chemotherapy dosing regimens for conditioning based on their age and other significant co-morbidities as assessed by the treating transplant physician. Two conditioning regimens exist for treatment which vary in their doses of fludarabine and melphalan. There are also two variations for immunosuppression based on whether the patient has a 10/10 donor or a 9/10 donor. The two conditioning regimens and two concurrent immunosuppression options are detailed below in Tables 5 through 8.

- REGIMEN 1: Flu/Mel conditioning option for patients ≤ 55 years with 10/10 matched donor (related or unrelated)

TABLE 5: Flu/Mel conditioning for patients ≤ 55 years

Day #	Agent	Management plan
-6	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-5	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-4	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-3	Fludarabine Melphalan Cyclosporine Sirolimus*	Fludarabine 25 mg/m^2 iv over 30 minutes Melphalan 70 mg/m^2 iv Start cyclosporine 5 mg/kg PO bid Start sirolimus 2 mg PO bid (target 3-12 ng/ml)
-2	Fludarabine Melphalan	Fludarabine 25 mg/m^2 iv over 30 minutes Melphalan 70 mg/m^2 iv
0	Graft infusion Mycophenylate mofetil	Infuse donor bone marrow or peripheral blood Start mycophenylate mofetil (MMF) 15 mg/kg PO tid
+30	MMF	Change MMF to 15 mg/kg PO bid
+40	MMF	Stop MMF
+96	Cyclosporine	Taper cyclosporine until day +150
+150	Sirolimus*	Taper sirolimus until day +180

- REGIMEN 2: Flu/Mel conditioning for patients > 55 years or with significant co-morbidities with 10/10 matched donor (related or unrelated)

TABLE 6: Flu/Mel/TBI conditioning for patients > 55 years or with significant co-morbidities

Day #	Agent	Management plan
-6	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-5	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-4	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-3	Fludarabine Cyclosporine Sirolimus*	Fludarabine 25 mg/m^2 iv over 30 minutes Start cyclosporine 5 mg/kg PO bid Start sirolimus 2 mg PO bid (target 3-12 ng/ml)
-2	Fludarabine Melphalan	Fludarabine 25 mg/m^2 iv over 30 minutes Melphalan 100 mg/m^2 iv
-1 or 0	Total body irradiation	2 or 3 Gy TBI
0	Graft infusion Mycophenylate mofetil	Infuse donor bone marrow or peripheral blood Start mycophenylate mofetil (MMF) 15 mg/kg PO tid
+30	MMF	Change MMF to 15 mg/kg PO bid
+40	MMF	Stop MMF
+96	Cyclosporine	Taper cyclosporine until day +150
+150	Sirolimus*	Taper sirolimus until day +180

* Note regarding sirolimus: This drug will only be added in for “triple” immunosuppression for patients who have matched unrelated donors. Patients with matched sibling donors will receive MMF and cyclosporine alone.

- REGIMEN 3: Flu/Mel conditioning option for patients ≤ 55 years with 9/10 donor

TABLE 7: Flu/Mel conditioning for patients ≤ 55 years

Day #	Agent	Management plan
-6	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-5	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-4	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-3	Fludarabine Melphalan Cyclosporine Sirolimus	Fludarabine 25 mg/m^2 iv over 30 minutes Melphalan 70 mg/m^2 iv Start cyclosporine 5 mg/kg PO bid Start sirolimus 2 mg PO bid (target 3-12 ng/ml)
-2	Fludarabine Melphalan	Fludarabine 25 mg/m^2 iv over 30 minutes Melphalan 70 mg/m^2 iv
0	Graft infusion Mycophenylate mofetil	Infuse donor bone marrow or peripheral blood Start mycophenylate mofetil (MMF) 15 mg/kg PO tid
+30	MMF	Change MMF to 15 mg/kg PO bid
+100	MMF	Taper MMF until day +150
+150	Cyclosporine	Taper cyclosporine until day +180
+180	Sirolimus	Taper sirolimus until day +365

- REGIMEN 4: Flu/Mel conditioning for patients > 55 years or with significant co-morbidities with 9/10 donor

TABLE 8: Flu/Mel/TBI conditioning for patients > 55 years or with significant co-morbidities

Day #	Agent	Management plan
-6	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-5	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-4	Fludarabine	Fludarabine 25 mg/m^2 iv over 30 minutes
-3	Fludarabine Cyclosporine Sirolimus	Fludarabine 25 mg/m^2 iv over 30 minutes Start cyclosporine 5 mg/kg PO bid Start sirolimus 2 mg PO bid (target 3-12 ng/ml)
-2	Fludarabine Melphalan	Fludarabine 25 mg/m^2 iv over 30 minutes Melphalan 100 mg/m^2 iv
-1 or 0	Total body irradiation	2 or 3 Gy TBI
0	Graft infusion Mycophenylate mofetil	Infuse donor bone marrow or peripheral blood Start mycophenylate mofetil (MMF) 15 mg/kg PO tid
+30	MMF	Change MMF to 15 mg/kg PO bid
+100	MMF	Taper MMF until day +150
+150	Cyclosporine	Taper cyclosporine until day +180
+180	Sirolimus	Taper sirolimus until day +365

8.5 Conditioning regimen

8.5.1 Donors

Matched related donors will typically receive G-CSF conditioning beginning at Day -5. G-CSF will be administered per transplant standard practice, which is 16 µg/kg/day, subcutaneously. On Day -1, peripheral blood stem cells (PBSC) will be collected from the donor and stored at -4ºC overnight. If there are fewer than 5x10^6 CD34+ cells per kg of recipient weight in the Day -1 collection, a second collection of PBSC will occur on Day 0, and both collections will be transfused on day 0.

8.5.2 Recipients

The **reduced-intensity conditioning regimen** will consist of fludarabine and melphalan. Because of increased toxicity noted with the Flu/Mel conditioning regimen recently noted at UW/FHCRC, the dose of melphalan will be decreased to a one-time dose of 100mg/m^2 for patients >55 years of age, or with significant co-morbidities (at investigators' discretion). The dosing schedule is described in TABLES 5 and 6 above.[23] Fludarabine and melphalan are commercially available. Infusion times are approximate. These medications should be stored and mixed according to the manufacturer's recommendations. Calculation of m^2 will be per Standard Practice Guidelines.

Fludarabine: Fludarabine will be administered once daily intravenously according to pharmacy standards. Fludarabine may cause bone marrow suppression, nausea, vomiting, diarrhea, stomatitis, rash, pneumonitis and neurotoxicity.

Melphalan: Melphalan will be infused once daily intravenously according to pharmacy standards. Melphalan can cause bone marrow suppression, nausea, vomiting, anorexia, stomatitis, hair loss, and weakness.

TBI: On day -1 or 0 (dependent on scheduling), 2 or 3 Gy of total body irradiation will be administered at 6-7 cGy/min from a linear accelerator. Regardless of the actual time of TBI administration on Day

0, immunosuppression should be given per schedule and prior to the infusion of stem cells. Dosimetry calculations are performed by the radiation therapist.

Criteria for 3 Gy TBI: Patients need to fulfill one or more of the following criteria for 3 Gy TBI:

a. Patients not previously treated with myelosuppressive chemotherapy prior to starting G-CLAM (e.g., patients who have received hypomethylating therapy alone)
b. Patients who have not had myelosuppressive chemotherapy prior to starting G-CLAM within 3-6 months of HCT may be at higher risk of rejection depending on treatment history and underlying diagnosis. Confirm TBI dose (200 vs 300 cGy) with PI.
c. Patients with AML or MDS with any measurable residual disease (by multiparameter flow cytometry) prior to HCT

Please refer to Standard Practice Guidelines for information about administration, toxicity and complications.

8.6 Acute GVHD prophylaxis

Triple immunosuppressive therapy per FH2448 (MMF, cyclosporine, and sirolimus) will be used for patients with matched unrelated donors; details follow and are available in TABLES 5 and 6 above. Double immunosuppressive therapy (MMF and cyclosporine) will be used for patients with matched sibling donors, with the same schedule but without sirolimus.

Protocol FH2448 used triple therapy with mycophenylate mofetil (MMF), cyclosporine, and sirolimus in a reduced-intensity conditioning protocol with fludarabine and TBI for matched unrelated donor transplants. The regimen will include MMF given at a dose of 15 mg/kg PO tid starting day 0 until day +30, then bid until day +40; cyclosporine given at a dose of 5 mg/kg PO bid starting day -3 until day +96, with a taper until day +150 (therapeutic target prior to taper as per table 9 below); and sirolimus, given at a dose of 2 mg PO daily, starting day – 3 until day +150, with a taper until day +180 (therapeutic target prior to taper 3-12 ng/ml). This regimen has been shown to be superior to an arm containing only MMF and cyclosporine in a randomized phase 3 study (FH2448). Patients with matched related donors will receive only MMF and cyclosporine.

Mycophenolate mofetil, cyclosporine, and sirolimus are commercially available. These medications should be stored and mixed according to the manufacturer's recommendations. Calculation of m^2 will be per Standard Practice Guidelines.

Mycophenolate mofetil (MMF): MMF will be given at a dose of 15 mg/kg PO tid based on adjusted body weight starting day 0 until day +30, then bid. The first dose will be given on day 0 in the evening after HCT (i.e., approximately 4-6 hours after HCT). Doses will be rounded to the nearest 250mg. If there is nausea and vomiting at any time preventing the oral administration of MMF, MMF should be administered IV based on adjusted body weight at 15 mg/kg q8hr. . If in the clinical judgment of the investigator the observed toxicity is related to MMF administration, a dose adjustment may occur. If severe refractory diarrhea, overt gastrointestinal bleeding, or neutropenia occurs, MMF may be temporarily stopped. The MMF should be restarted at 20% reduced dose when the underlying toxicity subsides. MMF will be stopped without taper per the schedules above unless GVHD or disease relapse/progression occurs.

Cyclosporine: Cyclosporine will be given at a dose of 5 mg/kg PO q12 hours from day -3, based on adjusted body weight. If there is nausea and vomiting at any time during cyclosporine treatment, the drug should be given IV at the appropriate dose that was used to obtain a therapeutic level. In the absence of acute or chronic GVHD, cyclosporine is tapered per the schedules above.

Blood pressure, renal function (Cr, BUN), electrolytes and magnesium will be followed at least three times per week during the first month, twice weekly until day +100, then once per week until cyclosporine is stopped. Whole blood trough levels of cyclosporine will be evaluated start on day 0 and twice weekly post-transplant during the first 28 days. After taper, dose levels will be measured weekly if stable.

Dose reductions should only be made if cyclosporine toxicity is present or levels exceed upper limits of target by 20%, in the absence of toxicity.

Cyclosporine side effects are generally reversible, and may include renal insufficiency, hypomagnesemia, paresthesias, tremor, seizures, visual disturbances, paresis, disorientation, depression, confusion, somnolence, coma, nausea, hypertension, hemolytic-uremic syndrome, hyperglycemia, gynecomastia, and hypertrichosis.

TABLE 9: Cyclosporine target trough levels and recommended dose adjustments.

	Cyclosporine target level
Day 0 to day +28	350 ng/ml
After day +28	120-300 ng/ml
Levels exceeding upper limits of target by >20% • **With or without cyclosporine toxicity** • **Decrease in GVHD ≥ 50%** • **Increase in creatinine 2x baseline due to cyclosporine**	25% dose reduction

Sirolimus Sirolimus should be given at least 4 hours after an oral dose of cyclosporine as concurrent administration leads to elevation of sirolimus levels. Sirolimus will be started on day -3 at 2mg every day orally through day +150. In the absence of GVHD, sirolimus should be tapered at day 150 by 25% per week for 4 weeks and discontinued on day +180. In the presence of GVHD or if the patient is receiving glucocorticoid therapy, continuation of sirolimus will be at the discretion of the attending physician. To minimize variability of exposure to sirolimus, the drug should be taken consistently with or without food. Grapefruit juice reduced CYP3A4-mediated metabolism of sirolimus and should not be administered with sirolimus or used for dilution.

Dosing will be adjusted to maintain a target blood level of 3-12 ng/ml. Dose adjustments are based on clinical toxicity, blood levels, and GVHD. The dosage should be adjusted if the patient vomits within 15 minutes of taking a dose. Premedication with antiemetics is acceptable if vomiting occurs. Taper will occur as per the schedules above.

Refer to the Standard Practice Guidelines for additional information regarding the use of MMF, cyclosporine, and sirolimus for GVHD prophylaxis.

9. SUPPORTIVE CARE

Patients will receive transfusions, infection prophylaxis, and therapy according to standard practice guidelines. Supportive care will be determined by the physicians from the leukemia and transplant teams caring for the patient.

10. PATIENT REPORTED OUTCOMES AND RESOURCE UTILIZATION

Patient-reported outcomes and resource utilization – If we proceed to a randomized trial, we will incorporate measurement of patient-reported outcomes and resource utilization. Hence, we wish to pilot collection of these data in this trial. Patient-reported outcomes (PROs) will include:

1) the 27 item FACT-G comprised of physical, emotional, social and function well-being subscales
2) FACT-Leuk (which includes the FACT-G, as well as the Leukemia subscale with 17 items)
3) the FACT-BMT subscale, composed of 10 scored items in the BMT subscale
4) the MD Anderson Symptom Inventory
5) the EuroQOL-5D – 5 items that allow calculation of utility, a factor used for cost-utility (effectiveness) analysis.

Patient-reported outcomes will be collected at enrollment (including sociodemographics, information about their caregiver situation, and patient-defined goals of care), then after completion of re-induction chemotherapy (day 10 +/- 3 days). For patients who undergo HCT regardless of timing, PROs will be collected just prior to HCT conditioning and at 6 and 12 months after HCT (if possible). These questionnaires are expected to take 10-15 minutes to complete. Many patients live outside the Seattle area, so study staff will mail questionnaires to patients up to two times before declaring that the patient has not responded; lack of response will be documented and will not count as a deviation from study procedures. Resource utilization for the 12 months after enrollment will be obtained from the administrative systems at the Seattle Cancer Care Alliance and University of Washington Hospitals. Certain costs will not be captured such as professional fees, outpatient pharmacy, and care delivered outside the study site.

11. GUIDELINES FOR SERIOUS ADVERSE EVENT REPORTING

11.1 Expedited reporting requirements.

In accordance with FHCRC/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within ten (10) calendar days of learning of the problem. Both the “Expedited Reporting Form for Unanticipated Problems or Noncompliance” and the “Adverse Event Reporting Form”, or equivalent forms, will be completed for this reporting.

11.2 Definitions

Adverse Event (AE): Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure whether or not considered to be related. Mechanisms of obtaining information on AE include monthly transcripts, assessment forms obtained after each clinic visit, and hospital progress and discharge notes. Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate.

Related or Possibly Related AE: An AE is “related or possibly related to the research procedures” if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not “related or possibly related”. If there is any question whether or not an AE is related or possibly related, the AE should be reported.

Serious AE (SAE): An adverse event that results in any of the following outcomes:

- Death
- Life-threatening adverse event (real risk of dying)
- Prolongation of hospitalization*
- Persistent or significant disability/incapacity/or change in psychosocial status
- Congenital anomaly
- Requirement of intervention to prevent permanent impairment of damage

*Hospitalization itself will not be considered a serious adverse event if required for complications of AML or comorbid conditions. Hospitalization will be considered a SAE if it fulfills the criteria for a serious and unexpected adverse event as otherwise described.

Unexpected AE: An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the known of foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document, and other relevant sources of information such as product labeling and package inserts.

Myelosuppression and associated complications are expected events during leukemia chemotherapy and allogeneic transplant; therefore, myelosuppression and associated expected complications such as fever, infections, bleeding, and related hospitalizations will be summarized in the annual report to the IRB. Therefore, in this study, we expect to monitor closely and report promptly on AEs that are serious, related, and unexpected.

AE monitoring will begin on Day 1 of GCLAM therapy or the date of consent, whichever date comes first. AEs will continue to be monitored until the following timepoints:

- For subjects who are "successes," AEs will be followed up to day 100 after transplant.
- For subjects who are "failures" and do not receive transplant within 60 days, AEs will be followed only until the date the subject is off-study.

TABLE 10: Schedule of study assessments

Procedure	Pre-study screening[1]	Induction	Pre-HCT	HCT	Post-HCT
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics (age, race/ethnicity, gender)	X				
Physical exam, ECOG PS, height, weight, vitals	X				
Pregnancy test (quantitative HCG)[2]	X				
GCLAM chemotherapy[3]		X			
Fludarabine/melphalan				X	
GVHD prophylaxis[4]				X	X
Bone marrow evaluation	X[5]		X[6]		
TRM evaluation				X	X
Formal organ function testing[7]			X		
Patient-reported outcomes[8]	X		X		X
Monitoring of SAEs[9]		X	X	X	X

[1] All pre-study screening must be done within 30 days of signing consent unless otherwise specified.
[2] Women of age <60 will be considered for pregnancy testing prior to enrollment. If potential female participants have not had menstrual bleeding in >2 years prior to enrollment, pregnancy test will not be required.
[3] Please note that GCLAM induction chemotherapy may start prior to consent. Additionally, G-CSF will start 24 hours prior to chemotherapy (i.e., day 0).
[4] The GVHD prophylaxis regimen will be dosed per tables 5, 6, 7, and 8.
[5] Bone marrow evaluation will routinely be done to establish eligibility but does not need to be repeated for the study.
[6] Timing of bone marrow evaluation will be left to the discretion of the treating physician, but should preferably be done within 7 days of beginning HCT conditioning. *Results of bone marrow evaluation will not affect ability of patient to move on to allogeneic HCT*.
[7] See section 3 for full inclusion/exclusion criteria. Patients will have organ function assessed prior to proceeding to HCT: heart (echocardiogram or MUGA), lungs (pulmonary function testing), kidneys (GFR), and liver (bilirubin, ALT).
[8] See section 10 for details. Patient-reported outcomes will be collected at enrollment, day 10 after initiation of induction chemotherapy +/- 3 days, prior to HCT, and at 6 and 12 months post-HCT.
[9] SAEs will be routinely monitored and reported to the IRB.

12. STATISTICAL CONSIDERATIONS

12.1 Sample size calculation

As noted in Section 2A, only 62/583 (11%) patients presenting with R/R AML over the 7 year period 2008-2015 received HCT within 60 days of their presentation as initial treatment, i.e. 7 patients per year. Our ultimate goal is to launch a study that will randomize patients between early HCT and the late approach of HCT only once CR or CRp/CRi +/- MRD has occurred. We anticipate that a randomized trial would require at least 40 patients (20/arm, assuming median survival is 6 months with the standard approach and is 12 months with early HCT, testing with a one-sided alpha value of 10% and 80% power). Before undertaking a randomized trial, we propose this feasibility trial to assess the feasibility of accruing to such a study and of transplanting patients quickly enough to make a randomized trial feasible.

We would consider this feasibility study a success and plan to launch a randomized trial if: 1) we were able to enroll 30 patients per year (1/3 of the anticipated 90 who present with R/R AML), and 2) we transplant at least 15 of the 30 patients within 60 days of start of induction therapy, and 3) among patients who are transplanted the observed 6-month relapse-free survival after transplant is 40% or higher. As noted in Background, we anticipate that 35 patients with R/R AML per year will have donors already identified when found to have R/R AML at FHCRC, so we believe accrual to the trial is feasible. The expected 6-month relapse-free survival rate for patients not undergoing early HCT is 10% (personal communication, E. Estey and S. Buckley, based on 246 patients receiving GCLAM without early transplant in the last 3 years at the Center).

Early stopping of the accrual to this study will be monitored for relapse-free survival (RFS) and acute GVHD (GVHD graded III or IV) at day 100 after transplant. Based on the poor outcomes for this patient population without early transplant, we would find an observed day 100 RFS rate of 30% or higher acceptable and want to place the study on an enrollment hold to review potential corrective actions if the observed day 100 RFS rate is lower than 30%. Based on aGVHD data from the center we would find an observed aGVHD rate of 25% or lower acceptable and would want to place the study on an enrollment hold to review potential corrective actions if the observed day 100 aGVHD rate exceeds 25%. Based on these criteria, the stopping rules will be used:

Number of transplanted patients	Number of RFS events for early stopping (stop if observe at least the number of events below)
7	5
8	6
9-10	7
11	8
12	9
13-14	10
15	11
16-17	12
18	13
19-20	14
21	15
22	16

23-24	17
25	18
26-27	19
28	20
29-30	21

Number of transplanted patients	Number of aGVHD events for early stopping (stop if observe at least the number of events below)
8-11	3
12-15	4
16-19	5
20-23	6
24-27	7
28-30	8

RFS and aGVHD will be monitored independently. If either endpoint has a number of events for stopping early, the trial will pause to review potential corrective actions regardless of the outcomes with the other endpoint.

All events which qualify toward meeting stopping rules will be reviewed at study steering committee meetings as detailed in section 13.0. All decisions involving enrollment pause or termination, as well as implementation of any corrective actions, will be first reviewed by the steering committee.

12.2 Endpoint definitions

- Early transplant – infusion of an allogeneic graft less than 60 days after initiation of re-induction chemotherapy
- Remission - <5% blasts on bone marrow biopsy with hematologic recovery, defined as ANC>1000/ul and platelets >100,000/ml
- CRi – complete remission with insufficient hematologic recovery, defined as ANC < 1000/ul or platelets < 100,000/ul
- CRp – complete remission but platelets < 100,000/ul
- Minimal residual disease – any detectable disease by flow cytometry, cytogenetics, FISH or PCR in a patient otherwise fulfilling remission criteria
- Relapse – >5% blasts in bone marrow, flow cytometry, or manual differential OR treatment for active relapsed disease. Prophylaxis against relapse or treatment for MRD (including donor lymphocyte infusion, genetically modified T cells or withdrawal of immunosuppression) will not be considered relapse for the purposes of this trial.

12.3 Analysis plan

Principal objective: If the definition of feasibility in met as defined in Section 12.1, the study will be considered feasible.

Secondary objectives: as this is a feasibility study, all analyses will be descriptive in nature.

1. Overall survival relapse-free survival and event-free survival will be estimated with the Kaplan-Meier method. Cumulative incidence of aGVHD and TRM will be calculated. Remission rates will be tabulated. These endpoints will be estimated for all patients who receive early transplant, and all endpoints applicable to the full study cohort (survival endpoints and remission rate) will be estimated in the full study cohort.
2. We will compare patients who receive early HCT to those that don't using Fisher's exact test for categorical variables (e.g., gender) and the Wilcoxon rank sum test for quantitative variables (e.g., age).
3. Patient-reported outcomes and resource utilization will be summarized descriptively. The amount of missing data will be summarized for each type of data using percent collection from surviving patients for PRO timepoints and description of days of hospitalization (the major driver of costs within the first year) for resource utilization.
4. The treatment course and outcomes for patients who enrolled and had allogeneic HCT off-study will be described

.

Exploratory objective: We plan to identify one patient not enrolled on this study, transplanted with standard scheduling the past 5 years, matched on age (within +/- 5 years), relapse status (refractory, relapse with 1 prior CR, relapse with more than 1 prior CR). We will then compare outcomes between patients who received transplant on this study with the matched patients. Log-rank tests and Cox regression will be used for survival outcomes. Cumulative incidence regression will be used to compare outcomes subject to competing risks (acute GVHD and TRM).

13. DATA AND SAFETY MONITORING PLAN

The Principal Investigator will carry out ongoing trial oversight. The study team will meet regularly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. All investigators on the protocol have received formal training in the ethical conduct of human research.

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Previous versions of the protocol specified that a Data Safety and Monitoring Board (DSMB) would also be assembled. As of June 2017, monitoring of the study will primarily be taken over by the bodies described above (DSMC, SRC, and IRB). The previous DSMB will continue to convene as a steering committee approximately quarterly to help with study oversight and planning. This steering committee will include the Principal Investigator (as a consulting member), research coordinator, data manager and three faculty members from within the UW/FHCRC Cancer Consortium. These three faculty members must practice outside of the AML Disease Group. The steering committee will meet to discuss safety of protocol participants, validity and integrity of the data, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

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