FHCC Protocol 2186 Statistical Analysis Plan
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FHCC Protocol 2186:

Title: Hematopoietic Bone Marrow Transplantation for Patients with High-Risk Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), or Myelodysplastic Syndrome (MDS) using Related HLA-Mismatched Donors: A Trial Using Radiolabeled Anti-CD45 Antibody Combined with Immunosuppression Before and After Transplantation

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12.0 STATISTICAL CONSIDERATIONS

12.1 Dose-Finding and Suspension Rules

This is a Phase I dose-escalation study whose primary objective is the estimation of the MTD of radiation delivered to normal organs by 131I-BC8 Ab when combined with FLU/CY, and 2 Gy TBI followed by HCT from related, HLA-haploidentical donors. For this group of patients at extremely high risk of relapse after marrow transplantation, it is reasonable to accept a rate of grade III/IV regimen-related toxicity as high as 25% if anti-leukemic efficacy is improved by the therapy. Thus in this study we will define the MTD as the dose that is associated with a true Grade III/IV RRT rate of 25%, and the dose escalation/de-escalation schema is based upon this target toxicity rate. We anticipate treating 25 to 50 patients, with the final number treated dependent upon the extent of dose escalation and the number of patients treated at each dose level to achieve a minimum of 20 patients evaluable for RRT in the second phase of the trial. If a patient(s) is available for study enrollment prior to all 4 patients in a cohort being fully evaluated for DLT, such a patient will be treated at the current dose level. The outcome of this patient with respect to DLT will not impact the decision of what dose to treat the next cohort. However, such patients will be used in the estimation of the MTD at the conclusion of the second stage (as detailed in section 12.2).

A secondary objective of this study is to examine whether engraftment can be achieved safely among patients with high-risk hematologic malignancies who undergo non-myeloablative HCT from related, HLA-haploidentical donors. In a recent study by Luznik, et al. (submitted for publication and see Background section of protocol), 15/84 (18%) haploidentical patients with at least 2 mismatched antigens experienced graft rejection. Based on these data, a rule for trial suspension will be put in place such that if sufficient evidence exists suggesting that the true rate of graft rejection exceeds 20%, the protocol will be suspended and reviewed by the investigators and other experts/committees as appropriate to determine whether the trial should be terminated, continued without change, or continued with revisions. Sufficient evidence will be taken to be a lower limit of the appropriate 80% one-sided confidence interval associated with the estimated proportion of rejections in excess of .20. These proportions and associated confidence intervals will be calculated after every 5th patient enrolled is evaluable. Operationally, graft rejection at any of the following observed proportions would trigger a suspension: 3/5, 4/10, 5/15, 6/20, 8/25, 9/30, 10/35, or 11/40 patients.

In addition to graft rejection, the study will be suspended if there is sufficient evidence to suggest that the true rate of grades III-IV acute GvHD at day +100 is excessive (graded according to the established criteria at the FHCRC). Sufficient evidence for grades III-IV GvHD will be taken to be an observed proportion of GvHD whose lower limit to the associated one-sided 80% confidence interval exceeds 35%. As with rejection, these proportions will be evaluated after every 5th enrolled patient becomes evaluable. Operationally, any of the following observed proportions of GvHD would lead to study suspension: 4/5, 6/10, 8/15, 10/20, 12/25, 14/30, 16/35, or 18/40.

Each suspension rule will be evaluated among all patients enrolled, regardless of the dose of antibody administered.

The following table summarizes the operating characteristics of each of these rules, each rule considered independent of the other.

Table 12.1 Characteristics of Suspension Rules

Number of Patients	True Rate of Graft Rejection	Probability of Suspension[1]	True Rate of GVHD	Probability of Suspension[2]
20	.15	.12	.25	.04
35	.15	.13	.25	.05
20	.35	.80	.50	.66
35	.35	.90	.50	.83

[1]Represents estimate of the probability of study suspension by associated number of patients due to excess graft rejection.

[2]Represents estimate of the probability of study suspension by associated number of patients due to excess GvHD.

Each estimated from 5,000 Monte Carlo simulations.

Activation of any stopping/suspension rule will be reported within 7 days of determination to the FHCRC IRB, study investigators, and FDA.

Because the anti-leukemic effect of 131I-BC8 Ab combined with this non-myeloablative regimen is unknown, but likely to increase at higher dose levels, we will follow disease response and duration of remission, but rates of relapse post-transplant, or failure to enter remission, will not halt the study.

12.2 Dose-Escalation/De-Escalation

A. Dose to Normal Organ

Dose escalation/de-escalation will be conducted by the "two-stage" approach introduced by Storer.[20] The maximum tolerated dose (MTD) will be defined as the dose that is associated with a true dose-limiting toxicity (DLT) rate of 25%. A DLT will be defined as a Grade III/IV (Bearman scale) toxicity that occurs within 30 days following transplant. The starting dose level will be a total isotope dose estimated to deliver Dose Level 6, 12 Gy to the normal organ receiving the highest dose. The estimated MTD of radiation delivered to the normal organ receiving the highest dose by I-131-BC8 Ab on our Phase I study (Protocol #1432) will be at least 24 Gy delivered to the liver. The primary objective of our Phase I study (Protocol #1432) has been to estimate the MTD of Iodine-131-labeled BC8 (anti-CD45) Ab, followed by FLU, TBI conditioning. The original version of this protocol stated that the two-stage design of Storer would be used to estimate the MTD, with 20 patients to be enrolled on the second stage. The only DLTs (i.e., toxicities that dictate the dose modifications) thus far observed have occurred at the highest dose level (26 Gy) visited in the second stage. However, Protocol #1432 combined I-131-BC8 Ab with FLU, TBI conditioning followed by matched related or unrelated peripheral blood stem HCT, whereas this protocol combines I-131-BC8 Ab with FLU, CY, and TBI followed by HCT using haploidentical allografting. Given the

differences in conditioning and stem cell donors utilized between the protocols, a conservative starting dose of radiation from Ab of 12 Gy will be employed in this study. We anticipate that the combined toxicity of this starting dose of 12 Gy delivered by I-131-BC8 Ab combined with FLU, CY, and 2 Gy TBI will be less than that of 24 Gy delivered by I-131-BC8 Ab combined with FLU and 2 Gy TBI.

Single patients will be entered on the first stage, and escalation by 2 Gy increments (in the radiation dose delivered to the normal organ receiving the highest dose – Table 12.2) will occur until a patient experiences a DLT, at which point the second stage will begin at the next lower dose level. If the first patient (i.e., at the starting dose level) has DLT, de-escalation will occur by 2 Gy increments (Table 12.2) until the first dose at which a patient does not have DLT, at which point the second stage will begin at that dose level.

In the second stage, patients will be entered in cohorts of 4 evaluable patients (i.e., patients surviving at least 30 days following transplant, or patients who clearly have Grade III/IV RRT during that time frame). If the current cohort is treated at dose level k, the next cohort will be treated according to the following: level k-1 if 2 or more DLTs are encountered in the cohort; level k if 1 DLT is observed within the current cohort; level k+1 if 0 DLTs are seen in the current cohort. These rules are followed until a minimum of 20 evaluable patients have been treated at the second stage and have been evaluated for DLTs. The dose level will be capped at 26 Gy, however, so that if zero DLTs are observed within a cohort of 4 patients treated at 26 Gy, the next cohort of patients will be treated at 26 Gy. At the highest dose level, de-escalation rules will continue to apply to cohorts of 4, such that the next cohort of patients will be treated at 24Gy if 2 or more DLTs are observed. It is possible that a patient will be entered on the protocol before a patient currently enrolled on Stage 1 or all 4 patients in a cohort in Stage 2 have been followed long enough (30 days post-transplant) to evaluate toxicity. Such patients will be treated at the current dose level and will be used for purposes of fitting the dose-response curve upon completion of the second stage. However, these patients will not be used for purposes of dose modification unless required in the interests of patient safety based on the clinical judgment of the principal investigator, nor will they be counted towards the required number of patients for completion of the second stage.

Following the completed observation of the final patient, a two-parameter logistic model will be fit to the data, thereby generating a dose-response curve based on the observed toxicity rate at the various dose levels visited. Based on this fitted model, the MTD is estimated to be the dose that is associated with a toxicity rate of 25%.

Table 12.2: Dose Levels for Escalation/De-Escalation

Dose Level	Gray delivered by ^{131}I-BC8 Ab to normal organ receiving the highest dose (liver)
1	2 Gy
2	4 Gy
3	6 Gy
4	8 Gy
5	10 Gy
6	12 Gy (starting dose level)
7	14 Gy
8	16 Gy
9	18 Gy
10	20 Gy
11	22 Gy
12	24 Gy
13	26 Gy

B. Dose to Bone Marrow and Graft Failure

Initially no patient will receive a dose of ^{131}I estimated to deliver more than 43 Gy to the marrow (5 Gy less than the 48 Gy from ^{131}I-BC8 Ab tolerated on Protocol #1432). Patients for whom the amount of ^{131}I required to deliver the stipulated dose to liver would result in the delivery of more than 43 Gy to marrow will have the ^{131}I dose limited to the amount which would deliver 43 Gy to marrow. If 0 of 3, or no more than 1 of 6 patients treated at this estimated dose to marrow experiences graft failure, we will then escalate in increments of 5 Gy to marrow in those patients as allowed by the marrow: liver radiation absorbed dose ratio (i.e., without exceeding intended estimated radiation absorbed dose to liver). The MTD of radiation dose to marrow will be estimated to be the dose below any dose where $\geq$ 2 patients of up to 6 treated experience graft failure.