THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

NK Cells with HLA Compatible Hematopoietic Transplantation for High Risk Myeloid Malignancies
2012-0819

Core Protocol Information

Short Title:	NK Cells with HLA compatible hematopoietic transplantation for high risk myeloid malignancies
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Full Title:	NK Cells with HLA Compatible Hematopoietic Transplantation for High Risk Myeloid Malignancies
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Version:	30
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Abstract

Objectives:

Primary Objective

- Assess the safety of infusing ex vivo expanded NK cells in patients receiving busulfan-fludarabine with an allogeneic HLA matched hematopoietic transplantation for myeloid malignancies. Two sources of NK cells could be studied, depending on what donor source is available: cells from the HLA matched related donor or cells from an unrelated cord blood unit.
- For each source of NK cells we will determine:
    - the maximum tolerated cell dose,
    - the phenotype and function of the ex vivo expanded NK cells and their survival in vivo and
    - the rate of engraftment, graft-vs.-host disease (GVHD), immune reconstitution, relapse rates and survival for patients receiving this regimen.

Rationale: (Be as concise as possible)

The study will test hypothesis is that the addition of ex vivo expanded NK cells will improve eradication of myeloid malignancies when added to a regimen of busulfan-fludarabine and allogeneic hematopoietic transplantation. NK cells from different sources may potentially be used, each with different potential effects and toxicities. The initial study will determine the safety and toxicities of NK-cells from the HLA matched donor or an unrelated cord blood unit. Transplant outcomes will be compared with historical controls receiving the same regimen without NK cells.

Natural killer cells are a unique class of lymphocytes, with cytotoxic, and immunoregulatory function with potent antileukemia effects. NK cells are regulated by KIR receptor-ligand interactions and mediate cytotoxicity against certain HLA class I mismatched targets. By the missing ligand model, killing of tumor cells by NK cells occurs when there is a missing signal (or missing self) on the target cells. NK cytotoxicity in vitro is greatest from an HLA mismatched donor, but also occurs with against HLA matched targets.

We performed a phase I study using unexpanded NK cells, selected from peripheral blood of normal donors. This approach is limited by the relatively small dose of NK cells, which can be obtained from a normal donor. The addition of NK cells did not increase toxicity associated with hematopoietic transplantation. We have developed a system for ex vivo expansion of NK cells, allowing large numbers to be manufactured from a small starting population obtained by venipuncture. This allows administration of up to 100 fold higher cell doses. We are now proposing to go forward with a phase I/II study of these ex vivo expanded NK cells, and determine which source of cells will be most promising to improve progression free survival in patients with high risk myeloid leukemias.

Eligibility: (List All Criteria)

Inclusion:

1) Patients with age </= 65 years with one of the following:
2) Acute myeloid leukemia who fail to achieve complete remission with one course of induction chemotherapy or after relapse. Patients must have less than 20% bone marrow or peripheral blood blasts.
3) Acute myeloid leukemia in first remission with any of the following high risk features defined as: (i) Adverse cytogenetics: -5, del 5q, -7, del7q, abnormalities involving 3q, 9q, 11q, 20q, 21q, 17, +8 or complex karyotype [> 3 abnormalities] (ii) Preceding myelodysplastic or myeloproliferative syndrome; (iii) Presence of high risk molecular abnormalities including FLT3 mutations, DNMT3A, TET2; ras; kit; (iv) FAB M6 or M7 classification; (v) treatment-related AML. (vi) residual cytogenetic or molecular abnormalities
4) Myelodysplastic syndromes with intermediate, high or very high risk R-IPSS score, CMML or therapy related MDS.
5) CML which: (i) failed to achieve a cytogenetic remission to tyrosine kinase inhibitor treatment or has a cytogenetic relapse; or (ii) has ever been in accelerated phase or blast crisis.

6) Patient must have an identified a HLA (A,B,C,DR) compatible related or unrelated donor who is age 16 years of age or older and weighs at least 110 pounds for the stem cell donation.
7) Zubrod performance status 0 to 2 or Karnofsky of at least 60.
8) Left ventricular ejection fraction >/= 45%. No uncontrolled arrhythmias or uncontrolled symptomatic cardiac disease.
9) FEV1, FVC and DLCO >/= 50% of expected, corrected for hemoglobin.
10) Adequate liver function: a. Bilirubin </= 1.5 mg/dl (unless Gilbert's syndrome). b. SGPT </= 200 IU/ml unless related to patient malignancy. c. Hepatitis B surface antigen negative and hepatitis C antibody negative. d. No evidence of chronic active hepatitis or cirrhosis. e. Patients with a history of hepatitis C, but have a negative viral load, are eligible. f. The protocol chairman will determine the eligibility of patients related to hepatic abnormalities.
11) Serum creatinine <1.5 mg%.
12) Patient or patient's legal representative, parent(s) or guardian able to sign informed consent. Patients aged 7 to <18 to provide assent.
13) Pediatric patients (age 7-18 years) will be entered only after 3 adult patients have been enterd without dose limiting toxicity.

Exclusion:

1) Uncontrolled infection, not responding to appropriate antimicrobial agents after seven days of therapy. The Protocol PI is the final arbiter of eligibility.
2) Pleural/pericardial effusion or ascites >1L.
3) Patients who are known to be HIV-seropositive.
4) Pregnancy: Positive pregnancy test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization.
5) Women of child bearing potential not willing to use an effective contraceptive measure while on study.
6) Patients who are known to have allergy to mouse proteins.

Are patients <18 years of age eligible to participate in this study? (●) Yes ( ) No

Studies that include children must meet the criteria for inclusion.

http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc

http://www.hhs.gov/ohrp/policy/populations/children.html

Additional Comment: N/A

Are participants >65 years of age eligible to participate in this study? ( ) Yes (●) No

Are pregnant women eligible to participate in this study? ( ) Yes (●) No

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?

( ) Yes (●) No

Disease Group:

Blood And Marrow Transplantation, Leukemia, Myeloproliferative Diseases

Treatment Agents/Devices/Interventions:

Busulfan, Cyclophosphamide, Filgrastim-sndz (Zarxio), Fludarabine, Interleukin-2, MESNA, NK Cell Infusion, Stem Cell Transplantation, Tacrolimus

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ Yes ◉ No

Is this a blinded or double-blinded study? ○ Yes ◉ No

Preparative Regimen
Prior to initiating chemotherapy in this study, all toxicities from prior systemic chemotherapy must be resolved at least to grade 1. Flt3 or TKI inhibitors as well as intrathecal therapy, nonmyelosuppressive agents, low dose cytarabine, hydroxyurea are permitted if indicated to control active leukemia, but must be stopped at least 5 days prior to administering the PK-test dose of IV Busulfan to avoid pharmacologic interference with IV Busulfan.The source of NK cells does not change the preparative regimen and it is standard of care.

Busulfan test dose
The Busulfan therapeutic dose will be determined based upon pharmacokinetic testing using a test dose done within 2 weeks of the preparative regimen. The Busulfan test dose can be administered as an outpatient or as an inpatient. The Busulfan "test dose" of 32 mg/m^2 will be based on actual body weight. The infusion time will depend on the AUC – 60 min for AUC 4000 and 45 min for AUC 6000.

D-13 to D-10 Fludarabine and Busulfan administration
Fludarabine 40 mg/m^2 will be dosed per actual body weight/actual body surface area. No arbitrary dose adjustment(s) based are allowed. Fludarabine is administered IV once daily for 4 consecutive days, followed by the Busulfan dose.

Busulfan adjusted dose is determined to achieve a systemic exposure represented by an average daily AUC of 6000 microMol-min ± 5% for the entire 4-day treatment period. Patients over age 60 and/or with performance status=2 will receive AUC of 4000 microMol-min ± 5% for each dose. If it is not feasible to perform the pharmacokinetic studies, a Busulfan dose of 130 mg/m^2 should be administered (100 mg/m^2 for age over 60 or PS=2).

The PK-guided daily high-dose Busulfan dose(s) will be started immediately upon completion of the daily Flu doses.

D-8 Alloreactive NK infusion
Patients are premedicated with diphenhydramine 25 mg IVPB. Corticosteroids will not be administered as premedication. Epinephrine and antihistamines will be available at the patient's bedside during the NK cell infusion to help treat any allergic reaction that might occur.

The alloreactive NK cell infusion will be given at one of 4 dose levels based on the number of NK cells (CD3-,CD 56+ cells)/kg recipient body weight. Dose levels are: 10^6, 10^7, 3 x 10^7, 10^8.

For recipients who weigh > 100 kg, the NK cell dose will be determined as if their body weight is 100 kg.

Patients are premedicated with diphenhydramine 25 mg IVPB. Epinephrine and antihistamines will be available at the patient's bedside during the NK cell infusion to help treat any allergic reaction that might occur. For infusion, a normal saline intravenous drip will be established. The alloreactive NK cells will be infused through this line without a filter under direct supervision of the investigator or physician designee.

Contingencies: If the planned alloreactive NK cell product cannot be infused for any reason, such as the product not meeting release criteria, patients will skip the scheduled interleukin 2 administration and continue the treatment plan as indicated for day -3, i.e., Thymoglobulin 1.5 mg/kg for 3 days and PBSC transplantation. (i.e., days -8 to -4 will be deleted from the schedule). These patients are considered technical failures of the procedure.

If the cell product contains greater than 10^6 NK cells/kg, but less than the specified cell dose, the cells will be infused, and evaluated on an intent to treat basis.

Unused NK cells not required for the described assays will be discarded.

If a positive sterility culture is noted after infusion, the physician and the patient will be notified, antibiotic sensitivity of the organism will be determined. The patients will be evaluated with a blood culture and other studies as clinically indicated and receive antibiotic treatment as indicated. Patients will be monitored for evidence of infection. The FDA and the IRB will be notified and the laboratory will investigate the source of contamination.

D-8 to D-4. Systemic Interleukin-2 treatment
Patients receive systemic interleukin-2 at a dose of 0.5 million units subcutaneously for 5 doses. The doses are given approximately daily starting on day -8 (approximately 2 hours after NK cell infusion and after resolution of any infusion related toxicities) to day -4 to enhance the survival and cytotoxicity of the infused NK cells. Because of scheduling related to the NK cell infusion, it may be necessary to give 2 doses of IL-2 within 24 hours; however doses of IL-2 should not be given within 6 hours of the previous dose.

D0. Hematopoietic Stem Cell infusion
Peripheral blood progenitor cells will be infused on day 0 or on arrival of the unrelated donor cells. Premedication for the infusions will be per standard SCTCT department procedures.

Prophylaxis and Supportive Care as per standard practice in patients receiving allogeneic transplant and Stem Cell Transplantation and Cellular Therapy Guidelines, using post transplant cyclosphosphamide and tacrolimus.

Patients with chronic myeloid leukemia or Philadelphia chromosome positive acute leukemia may receive tyrosine kinase inhibitors as clinically indicated.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 72
Estimated monthly accrual at MDACC: 2-3

Screening Accrual:

Does this study include a screening component? No

Accrual Comments:
For each group, the maximum sample size will be 24, for up to 12 cohorts of 2 patients each, consequently the maximum sample size in the entire study thus will be 3*34=72 patients.

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

This study will be conducted on the Department of Biostatistics Clinical Trial Conduct (CTC) website.

This is a phase I/II dose-finding study to determine an optimal NK cell dose in each of three distinct patient subgroups, A = KIR mismatched haplo donors, B = KIR mismatched cord blood donors, C = matched SIB donors. The same dose-finding design will be used within each subgroup. Initial safety data from the Phase I study will be collected in an initial cohort of several adult subjects prior to enrolling any pediatric subjects.

Within each donor type subgroup, dose-finding will be done as follows. The Bayesian model averaging continual reassessment method, BMA-CRM, (Yin and Yuan, 2009) will be applied. The four NK cell doses to be studied are: 10^6, 10^7, 3 x 10^7, and 10^8 NK cells. Cohorts of 2 patients will be used, starting at the lowest NK cell dose level. Dose-limiting toxicity (DLT) is defined as any of the following events occurring through day 42: Graft failure, severe (grade 3,4) infusional toxicity, grade 3 organ toxicity that is in excess of the expected frequency for institutional norms, severe grade 4 organ toxicity, or death. The targeted toxicity probability for applying the BMA-CRM is 0.50. For each group, the maximum sample size will be 24, for up to 12 cohorts of 2 patients each, consequently the maximum sample size in the entire study thus will be 3*24=72 patients. Two safety rules will be applied. 1) no untried dose may be skipped when escalating and 2) if the lowest dose is unacceptably toxic (unsafe), then accrual in that subgroup will be terminated early and no dose selected. Formally, denoting the probability of toxicity at the lowest dose level by p1, the lowest dose will be considered unsafe if Pr{p1 > .50 | data} > .80. If all three subgroups are due to safety terminated, the trial will be stopped. Note: Effective 12/15/15, the haploidentical NK cell group was terminated to allow the study to focus on the two remaining groups.

BMA-CRM Model. To compute posterior probabilities of toxicity for each dose in subgroup, we adopt the models in Yin and Yuan (2009) with the recommended prior distributions therein. The two sets of probability rates for the four doses, which were averaged, used in the simulation were (0.30, 0.40, 0.50, 0.60) and (0.10, 0.20, 0.30, 0.40). Simulation results establishing the design's properties for each subgroup under each of five potential dose-toxicity scenarios are summarized in Table 1. Each scenario was simulated 2000 times. For each scenario, the table includes the true probability of toxicity, pT, the proportion of trials that each dose was selected, and the average number of patients treated at each dose.

Table 1. Operating Characteristics of the Design for Each Donor Type Subgroup

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	None
1	True pT	0.30	0.40	0.50	0.60	
	Selection %	5	32	**44**	17	3
	Avg. # Patients	5.3	7.7	7.3	3.3	
2	True pT	0.10	0.20	0.30	0.40	
	Selection %	0	1	15	**85**	0.0
	Avg. # Patients	2.5	2.8	5.4	13.4	
3	True pT	0.60	0.70	0.80	0.90	
	Selection %	28	8	0	0	**63**
	Avg. # Patients	11.1	3.0	0.5	0.0	
4	True pT	0.10	0.30	0.50	0.70	
	Selection %	0	12	**70**	18	0
	Avg. # Patients	2.5	5.1	11.2	5.2	
5	True pT	0.25	0.35	0.45	0.55	
	Selection %	2	21	**45**	31	1
	Avg. # Patients	4.2	6.3	7.9	5.4	
6	True pT	0.70	0.75	0.80	0.85	
	Selection %	12	2	0	0	**86**
	Avg. # Patients	8.8	1.4	0.2	0.0	
7	True pT	0.35	0.45	0.60	0.70	
	Selection %	9	**50**	31	3	7
	Avg. # Patients	6.9	9.3	5.5	1.2	

Patient Donor Type Assignment Algorithm

The following algorithm will be used to assign patient to the three donor groups {A,B,C} as they are accrued.

1. At the start of the study, all three subgroups are open.
2. If there are no acceptable doses within a subgroup (see below), the subgroup will be permanently closed.
3. Once 24 evaluable patients have been enrolled in a subgroup, the optimal dose will be chosen using the BMA-CRM criterion and the subgroup will be permanently closed.
4. If the current dose cohort of two patients is full and 0 or 1 out of the two patients have been evaluated for DLT at day 42, that subgroup will be considered temporarily closed.
5. Otherwise, the subgroup will be defined as open.

Patients will be assigned to the subgroup as they are enrolled using the following algorithm:

1. If all three subgroups are open, patients with a HLA matched sibling will receive NK cells from that donor.
2. Patients with an unrelated donor may receive NK cells from a cord blood unit, selected to provide the greatest KIR:KIR ligand mismatch.
3. If exactly one subgroup is open, new patients will be assigned to that subgroup.
4. If no subgroups are open, the enrollment of new patients must wait for at least one subgroup to open.

Secondary Outcomes. Secondary outcomes will include overall survival time, disease-free survival time, and GVHD. Grade 3 toxicities will be collected and we will determine if any occur in increased frequency compared to historical experience with this regime without NK cells.

Data Analysis. The data will be analyzed by fitting the CRM model to the final data and summarizing the posterior distributions of the probability of overall toxicity and of each adverse event in the definition of toxicity at the MTD and at the other doses, by tabulating the counts and rates of all secondary events both overall and cross-tabulated with dose, and fitting appropriate logistic or ordinal outcome regression models to assess possible patterns of change with dose.

Does this protocol include a dose expansion component? Yes

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
The study is not randomized or blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

Two safety rules will be applied. 1) no untried dose may be skipped when escalating and 2) if the lowest dose is unacceptably toxic (unsafe), then accrual in that subgroup will be terminated early and no dose selected. Formally, denoting the probability of toxicity at the lowest dose level by p1, the lowest dose will be considered unsafe if Pr{p1 > .50 | data} > .80. If all three subgroups are due to safety terminated, the trial will be stopped.

Protocol Monitoring Plan:

Patient registration and monitoring will be performed by the MD Anderson IND Office according to institutional policies.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MD Anderson
IND Number: 15436

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Immunotherapy

Is this an Immunotherapy study? No

Moon Shots Program

Will your protocol be funded by the Moon Shots Program? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: CPRIT grant (for AML patients) and CML Program Project Grant for CML patients titled, Adoptive Immunotherapy with NK Cells Expanded Ex Vivo for Treatment of Hematopoietic Malignancies.
Support Type: Grant Number(s): CPRIT MIRA Project 3 (RP110553-P3)

This Sponsor/Supporter/Granting Agency will not receive data.

Regulatory Requirements

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	No

Biosafety:

Does this study involve the use of Recombinant DNA Technology such as DNA nucleotide, RNA nucleotide, genetically modified human cells, animal cells, bacteria, or virus?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study involve human/animal tissue other than blood derived hematopoietic stem cells?	N/A

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- ( ) Yes
- (•) No
- ( ) Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? Yes

Please provide the name of the responsible party, the facility or department, contact information and the name of the product or intermediate.
The NK donor cells used in this trial will be processed in the GMP facility at MDACC.

Contact:
Elizabeth Shpall, MD
713-745-2161

Will you obtain an unlicensed (not FDA approved for use in humans) drug or biological product precursor or intermediate for use in patients? No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree? No