THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Trial of Immune Reconstitution with Activated T-Cells in Patients with Chronic Lymphocytic Leukemia (CLL)
2014-0830

Core Protocol Information

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Full Title:	Trial of Immune Reconstitution with Activated T-Cells in Patients with Chronic Lymphocytic Leukemia (CLL)
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Abstract

Objectives:

Primary Objectives:

1. To assess the feasibility and safety of infusion of autologous activated T-cells in patients with chronic lymphocytic leukemia.

Secondary Objectives:

1. To study immune reconstitution following infusion of activated T-cells in patients with chronic lymphocytic leukemia.
2. To study the incidence of infections for up to 1 year following activated T cell infusion.
3. To study the overall response rates.

Rationale: (Be as concise as possible)

Despite significant advances in the management of CLL the disease remains incurable with standard chemo-immunotherapy. Moreover, even after complete responses, immunological abnormalities and minimal residual disease remain in most patients. Ultimately, chronic immunosuppression resulting in infectious complications occurs in over 80% of CLL patients and is a major cause of mortality. The pathogenesis of infections in patients with CLL is complex and multifactorial. CLL in itself can cause disease related immunosuppression that is compounded by the immunosuppression induced by agents

like fludarabine and alemtuzumab that are commonly used in the treatment of this disease. In preliminary studies, T cells activated using CD3xCD28 co-stimulatory technology have been shown to reverse some of these immune defects. This procedure is based on the roles of the CD3 signaling complex and CD28 receptor in the activation of T cells. In this study we plan to give *ex-vivo* stimulated T-cell infusion to patients with CLL. The hypothesis is that infusion of *ex-vivo* expanded T cells will influence quantitative and functional immune reconstitution in these patients. This should result in reduced rate of infectious complications, secondary malignancies, and may delay the time to disease progression.

Eligibility: (List All Criteria)

Inclusion:

1) All patients must have a diagnosis of CLL by immunophenotyping and flow cytometry analysis of blood or bone marrow. 1) Patients must meet criteria for treatment based on the criteria proposed by NCI-sponsored CLL Working Group to include at least one of the following: a) weight loss of more than 10% over the preceding 6 months; or, b) extreme fatigue attributable to progressive disease; or, c) fever or night sweats without evidence of infection; or, d) worsening anemia (Rai stage III) or thrombocytopenia (Rai stage IV); or, e) massive lymphadenopathy (>10 cm) or rapidly progressive lymphocytosis (lymphocyte doubling time <6 months); or, f) prolymphocytic or Richter's transformation; or, 2) Patients with CLL who have received at least one prior line of therapy; or, 3) Patients with CLL who have frequent infections and/or recurrent secondary cancers.

2) No active CNS disease.

3) All patients must have a Karnofsky Performance Score > 60%.

4) Calculated creatinine clearance (by Cockroft-Gault) of > 50 ml/min.

5) Patients must not have untreated or uncontrolled life-threatening infection.

6) Patients must sign informed consent.

Exclusion:

1) Receipt of glucocorticoids (with the exception of inhaled glucocorticoid steroids for the use of allergic rhinitis or pulmonary disease) within 2 weeks of registration.

2) Autoimmune disease related to CLL, e.g., idiopathic thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia, is permitted if not requiring active treatment.

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

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:

Leukemia

Treatment Agents/Devices/Interventions:

T cell therapy

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ Yes ● No

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

All eligible patients will have 250 cc of whole blood collected via phlebotomy.

The collected blood will be expanded ex-vivo by aAPCs. The expansion will take 14 days. The process can generate 2.5×10^9 to 1×10^{10} cells which will be formulated for infusion in 100-500 mL of human serum albumin infusion buffer. Cells for later additional infusions may be cryopreserved.

Patients will receive a single infusion of *ex-vivo* expanded autologous T-Cells. Optimal dose will be 1×10^{10} activated T cells (+/- 20%), however for patients who cannot achieve that dose, a lower dose of activated T cells that meets release criteria may be infused at the discretion of the Principal Investigator.

Additionally, patients who have been previously treated on study, and subsequently need additional infusions may be retreated with previously cryopreserved expanded cells at the same or lower dose level. Retreatment will occur 6-12 months after the first infusion as long as no DLT was noted with the first infusion. These patients will be only followed for toxicity. Patients who have previously experienced DLT will be removed from the study and will not be eligible for retreatment.

Packaging and Administration
The T cells will be administered via intravenous infusion over 20-30 minutes without a leukocyte filter.

Autologous co-stimulated T-cell infusion

1. Co-stimulated T-cells will be infused at a dose of approximately 1×10^{10} (+/-20%). If optimal cell dose of 1×10^{10} (+/-20%).) is not achieved, a lower dose of activated T cells that meets release criteria may be infused at the discretion of the Principal Investigator.

2. Patients will receive premedication with Acetaminophen 650 mg PO and/or diphenhydramine 25-50 mg IV at least 30 minutes prior to infusion.

3. Additional orders: Acetaminophen 650 mg PO q4h for temperature > 38°, diphenhydramine 25 mg IVPB q3-4h prn and meperidine 25 mg IVPB q 2h prn for chills (if chills persist inform MD). Anaphylaxis precautions: Following drugs should be available at bedside: 3cc epinephrine 1:1000, diphenhydramine 25 mg IV and hydrocortisone 100 mg IV. In the event of a severe allergic reaction (e.g., anaphylaxis, bronchospasm, hypotension) or serious adverse reaction (i.e., cardiac failure, respiratory failure, severe nausea and vomiting) to the T Cell therapy, the infusion of the autologous T Cells will be stopped immediately and the patient will be provided with the supportive care deemed necessary by the physician and medical staff at the clinic.

4. Optional Procedure: With the patient's consent, if the patient cannot receive the co-stimulated T cells, the cells will remain cryopreserved in the Stem Cell Laboratory indefinitely. The patient can receive the cells at a later date. If the patient's physician feels that the patient will no longer benefit from the cells,

the cells may be used for research or discarded. If the patient refuses, the cells will be destroyed.

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

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC:	40
Estimated monthly accrual at MDACC:	1

Accrual Comments:
The sample size of 40 patients was chosen for logistical reasons.

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

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

Statistical Considerations:

Overview

This is a phase II trial of infusion of autologous T cells for immune restoration in patients with CLL. The primary scientific goal is to determine the feasibility and safety of this procedure. A total of 40 patients will receive T cell infusions. Endpoint evaluation will be at day +90 after the co-stimulated T cell infusion.

Sample Size

In this trial, the sample size of 40 patients was chosen for logistical reasons. With 40 patients, a 95% confidence interval around the success rate will be no wider than 32%.

Primary Endpoint

Success will be defined as achievement of a target activated T-cell dose of 1×10^8 +/- 20% and the lack of dose limiting toxicity (DLT).

For this trial DLT is defined as:

- Any grade 4 or higher non-hematologic toxicity or grade 3 or 4 allergy/immunology toxicity;
- Allergic reaction or urticaria grade 3 or higher (CTC v4.03 CTCAE) by +90 days after T cell infusion;
- Grade 2 or greater autoimmune phenomena; or,
- Grade 4 or higher hematologic toxicity (with the exception of any preexisting AE due to prior treatment or due to disease) deemed related to T cells and occurring by day +90 after T cell infusion.

Feasibility is defined as achievement of the target T cell dose (1×10^8 +/- 20%) without DLT in > 50% of patients enrolled.

Safety Monitoring

Any death due to the infusion of co-stimulated T-Cell product itself and not disease progression will be considered unacceptable and the study will be stopped. If the study is not terminated early, it will continue

until all patients have been treated with co-stimulated T Cells and completed all follow up evaluations.

In addition, we will use a Bayesian sequential monitoring rule to monitor the primary endpoint of the study. If there is a high probability that the overall success rate is less than 50%, enrollment into the trial will be stopped. We will enroll a minimum of 6 patients onto the study before stopping. We will use the following criteria: we will stop enrollment if at any time during the course of the trial:

Pr [90-day success rate > 0.50 | data] < 0.025

That is, if we determine that there is a less than 2.5% chance that the 90-day success rate is greater than 50%, accrual will be stopped. We assume a beta (1, 1) prior distribution for the success rate, which has a mean of 0.50 corresponding to the target success rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual if:

If there are this many patients accrued	**Stop the trial if this number of patients meet criteria for success**
6-7	0
8-10	0-1
11-13	0-2
14-15	0-3
16-18	0-4
19-21	0-5
22-23	0-6
24-26	0-7
27-28	0-8
29-31	0-9
32-33	0-10
34-35	0-11
36-38	0-12
39	0-13
40	Always Stop

This stopping rule was chosen to assure that the probability that the trial will stop early would be approximately 10% if the true success rate was 50%. The operating characteristics of this rule are shown in the table below.

We will enroll 3 patients and then wait till all 3 have reached +90 days without DLT before enrolling more patients. At that time point 3 additional patients will be enrolled and we will wait till they have all reached

+90 days and without DLT before enrolling the remaining patients.

Operating Characteristics for Success Monitoring Rule

If the true 90-day success rate is…	Early Stopping Probability	Achieved Sample Size		
		25th percentile	50th percentile	75th percentile
0.3	0.833	8	16	32
0.4	0.413	19	40	40
0.5	0.108	40	40	40
0.6	0.018	40	40	40
0.7	0.002	40	40	40

The monitoring rules will be assessed by the study team with assistance as necessary from the Department of Biostatistics at MD Anderson Cancer Center.

Secondary Analyses

Immune reconstitution: We will assess the percentages and absolute values of CD3+, CD4+, CD8+ and CD4/CD8 ratio and report these at each time point along with 95% confidence intervals. In addition, immune reconstitution will be compared at each time point.

Overall Response (CR+PR): We will assess overall response (CR+PR).

Infections: We will assess the rates of infection.

Criteria for Removal from Study:

1. "Subjects" voluntary withdrawal from protocol.
2. Noncompliance of the patient with protocol requirements
3. After 5 years of treatment completion
4. Subject lost to follow-up
5. Decision by the investigators that withdrawing is in the subject's best interest
6. Pregnancy
7. Termination of the study by the investigator, IRB, or FDA
8. Unacceptable toxicity and other safety reasons- as defined by the stopping rules below.
9. Patients who experience DLT will not be eligible for retreatment.

Toxicity Management, Stopping Rules and Study Termination

Only unexpected SAEs that are related to the activated autologous T cells would define a stopping rule.

Management of toxicity

Autoimmune toxicity associated with activated autologous T cells has been managed with a course of pharmacologic immunosuppression such as systemic corticosteroids.

Dose Limiting Toxicity
Dose limiting toxicity (DLT) is defined as any one or more of the following which occur after the T Cell Infusion:

1. Any Grade 3 or higher non-hematological adverse event other than fevers lasting less than 72 hours must will be considered DLT. Any prolonged grade 4 or higher hematologic toxicity (longer than 7 days) due to study treatment will be considered as DLT (CTC v4.03 CTCAE).

2. Allergic reaction or urticaria grade 3 or higher and deemed related to T cells (as determined using the Common Terminology Criteria for Adverse Events v4.03).

3. Grade 2 or greater autoimmune phenomena

4. Grade 4 or higher hematologic toxicity with the exception of any preexisting AE due to prior treatment or due to disease.

Stopping Rules
The statistical considerations section describes the primary stopping rule for the study, a rule which monitors patient success rate.

In addition, accrual to the study will be suspended to allow review with the institutional IRB if any death occurs among subjects who receive investigational agents due to the infusion of co-stimulated T-Cell product itself and not disease progression.

If the study is prematurely halted based on preliminary information, it will be allowed to continue only if it is determined upon review that the incidence of adverse events is not exceedingly high for this patient population and that any death is not primarily due to the co-stimulated T-Cell therapy. If the study is not terminated early, it will continue until all patients have been treated with co-stimulated T Cells and completed all follow up evaluations.

Data Safety Monitoring Board / DSMB at MDACC:

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

Please explain:
As of PDOL Version 07, this study is not randomized nor blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? Yes

Provide a summary or schedule of interim analysis.

We will use a Bayesian sequential monitoring rule (Thall et all (ref)) to monitor the primary endpoint of the study. See the Statistical Considerations section for details.

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: 16501

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

Moon Shots Program
Will your protocol be funded by the Moon Shots Program? Yes

Specific Disease Site(s): Chronic Lymphocytic Leukemia (CLL)

Platform(s): Applied Cellular Therapy (ACT)

Sponsorship and Support Information:

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

Sponsor Name: Moon Shot Program
Support Type: Other: CLL

This Sponsor/Supporter/Granting Agency will receive data.

Regulatory Requirements

Radioactive Material:

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

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	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?	Yes
Are you using Tisseel or Evicel or similar?	No

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 investigational agent to be administered under this protocol is activated autologous T cells manufactured by in the Cell Therapy Laboratory at the MD Anderson Cancer.

Contact:
Elizabeth Shpall, M.D.
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?	Yes

Obtained from a supplier under a manufacturing contract with MDACC

Student/Trainee Information:

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