THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Chemotherapy plus Ofatumumab followed by G-CSF for mobilization of peripheral blood stem cells in patients with non-Hodgkin's Lymphomas
2009-0796

Core Protocol Information

Short Title:	Stem cell collection with Ofatumumab
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Full Title:	Chemotherapy plus Ofatumumab followed by G-CSF for mobilization of peripheral blood stem cells in patients with non-Hodgkin's Lymphomas
Protocol Phase:	Phase II
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Abstract

Objectives:

Primary Objective:

To determine the feasibility of mobilization with ofatumumab + chemotherapy (collection of at least $2x10^6$ CD34+/Kg).

Secondary Objectives:

To determine the number of apheresis procedures, total stem cell yield/kg patient body weight and toxicity profile.

To assess the ability to purge malignant cells with ofatumumab.

To determine the degree of expression of various adhesion molecules and correlate with time to engraftment of neutrophils and platelets.

Rationale: (Be as concise as possible)

Relapse due to stem cell contamination by lymphoma cells and persistence of minimal residual disease remains the most common cause of failure after autologous transplantation for non-Hodgkin's lymphomas (NHL). Given its efficacy, its ability to deplete B cells and its limited toxicity, the anti-CD20 monoclonal antibody (MAb) rituximab has been incorporated into autologous transplantation strategies. We evaluated the efficacy and safety of administering high-dose rituximab in combination with high-dose BEAM (BCNU, etoposide, cytarabine and melphalan) conditioning and autologous transplantation in 67 patients with recurrent aggressive B-cell non-Hodgkin's lymphomas. Rituximab was administered during stem cell mobilization at 375 mg/m2 at 1 day before chemotherapy and 1000 mg/m2 at 7 days after chemotherapy and on day 1 and day 8 after transplant. For mobilization, patients received ifosfamide (10gm/m2 given by continuous infusion over 72 h days 1-3), and etoposide (150 mg/ m2, given intravenously, every 12 h for a total of 6 doses on days 1-3)). All patients received then G-CSF of 6 mcg/Kg subcutaneously, starting 24 h after completion of chemotherapy and continuing through the completion of apheresis. The results of this treatment were retrospectively compared with a historical control group receiving the same preparative regimen without rituximab. With the median follow-up time for the study group of 20 months, the two-year overall survival was 89% for the study group compared to 53% for control group (p=.002). The 2-year disease-free survival were 67% and 43%, respectively for the study group and control group (p=.004). However, patients with PET-positive scans at the time of transplant or had a high International Prognostic Index (IPI) did poorly. We have recently applied the same strategy in autologous transplantation for mantle cell lymphoma. This resulted in a marked improvement in progression-free survival for patients who received a transplant in their first remission (where a plateau emerged at 3-8 years) but did not change the outcomes for patients who received a transplant beyond their first remission. Recently, retrospective studies have also shown that patients who received rituximab during stem cell collection reduced the risk of relapse and improved survival also in follicular lymphoma .

Despite this fact, rituximab therapy is far from perfect; the infusion-related reactions are common, some of them are life-threatening, and patients will ultimately develop resistance following repetitive exposure to rituximab pre-transplantation. This may explain the suboptimal results observed in high-risk patients (PET-positive, high IPI, mantle cell beyond first remission, follicular lymphoma beyond their first relapse)

The CD20 antigen continues to be a great target for MAb therapy. Current research has shown that not all anti-CD20 MAbs are created equal. Ofatumumab has specific characteristics that differentiate it from rituximab, starting from a different binding site and binding properties to longer half-life and higher intensity complement-dependent cytotoxicity. Unlike rituximab, ofatumumab is also a fully humanized MAb with a low immunogeneic potential and, so far, formation of human anti-human antibodies has not been observed in patients exposed to ofatumumab. All these features allow shorter infusions with fewer infusion-related reactions than rituximab. Ofatumumab has also shown preclinical and clinical efficacy in different rituximab-resistant settings. Ofatumumab induced lysis in cells lines with low expression of CD20 and also has shown efficacy in cases of NHL that are primarily resistant or refractory to rituximab.

These features make ofatumumab an attractive product to be used in the setting of autologous transplantation for patients who have been exposed in the past to rituximab.

Eligibility: (List All Criteria)

Inclusion:

1) Patients with histologically confirmed CD20 positive B-cell NHL who are candidates for autologous SCT.
2) Patients must have PR to salvage chemotherapy.
3) Age 18-70 years.
4) Platelet count >/= 100,00 mm^3 independent of transfusion support.
5) Absolute neutrophil count >/= 1500/mm^3.
6) Zubrod performance status (PS) 2 or less.
7) Negative serum pregnancy test in women of childbearing potential. This is a female who has not been postmenopausal for at least 12 consecutive months or who has not undergone previous surgical sterilization.
8) Less than 5% marrow involvement with NHL within 4 weeks of study as defined by unilateral bone marrow aspiration and biopsy.
9) Seronegativity for HIV, HTLV1, Hepatitis .

Exclusion:

1) Subjects who have current active hepatic ((HbsAg, HbcAb, and positive viral load by PCR) or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment) with ALT > 2x upper limit of normal or bilirubin > 1.5. (Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.)
2) Active CNS disease.
3) Severe concomitant medical or psychiatric illness.
4) Lactating or breast feeding females.
5) Serum creatinine >1.6 mg/dl.
6) History of pelvic radiation.
7) Fludarabine-based chemotherapy within 6 months.

Is there an age limit? Yes

Why? Provide scientific justification:
The safety of autologous stem cell transplantation in patients > 70 years is not well established.

Disease Group:

Lymphoma

Treatment Agents/Devices/Interventions:

Etoposide, Ifosfamide, Neupogen, Ofatumumab

Proposed Treatment/Study Plan:

Mobilization chemotherapy/ofatumumab

- Ofatumumab will be given as per the following schedule, on days 1 (1000 mg) and 8 (2000 mg)
- Premedications

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment:

Table 1. Pre-medication Requirements prior to Ofatumumab Infusions:

Infusion #	Acetaminophen (po) or equivalent	Antihistamine (iv or po) diphenhydramine or equivalent	Glucocorticoid (iv) methylprednisolone or equivalent
1st	1000 mg	25 mg	80 mg
2nd	1000 mg	25 mg	80 mg

Infusion of Ofatumumab

Initial rate of the first and second infusion of ofatumumab will be titrated as per drug insert with the maximum rate of infusion not to exceed 200cc/hour. The dose on day 1 will not exceed 1000 mg. The dose on day 8 will not exceed 2000mg.

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Chemotherapy and Growth Factors

On Days 2, 3, and 4, patients will receive ifosfamide 3.33 gm/m2/day IV continuously and mesna continuously. Etoposide 150 mg/m2/dose IV will be administered every 12 hours on Days 2, 3, and 4. If central nervous system toxicity occurs with ifosfamide, the drug will be stopped, neurology consultation will be undertaken if needed, and other measures such as the use of methylene blue will be considered if necessary.

Ifosfamide and etoposide will be dosed on actual body weight unless the actual body weight is >40% over ideal body weight. In that situation an adjusted body weight will be used. Adjusted body weight : ((Actual body weight – ideal body weight) 0.5) + ideal body weight. Mesna dose is based on total dose of ifosfamide.

Patients will start G-CSF per standard of care starting on Day 6 until completion of aphresis.

Peripheral Blood Stem Cell Collection

Peripheral blood stem cell collection:

Upon recovery of counts peripheral blood stem cells will be collected using standard apheresis procedures. Apheresis will start when the CD34 counts reach 5-15 cells/ul. Although the target dose is 2 x 10^6/kg, patients would continue apheresis until >/= 4 x 10^6/kg is reached. If patients fail to mobilize adequate numbers of peripheral blood stem cells 28 days after starting Ofatumumab, they will be taken off study and treated as per the discretion of the treating physician. The last day of apheresis will be considered as the last day of active treatment on the protocol.

The apheresis products will be cryopreserved according to standard BMT cell processing procedures. 0.5 cc of the apheresis sample will be sent for flow cytometry to determine the CD34+ count and for evidence of monoclonal B cells.

A sample of peripheral blood (10 cc) will be evaluated for PCR for JH, bcl-2 (if follicular) or bcl-1 (if mantle cell). A sample of apheresis product (10 cc) will be sent to Dr. Reuben's lab for evaluation of dendritic cell population, natural killer cells and adhesion molecules by 2-color flow cytometry. All leftover samples will be destroyed.

Pretreatment Evaluation

- All tests to be done within 4 weeks of enrollment in the study:
- Complete history and physical examination
- CBC with differential, platelet count, PT, PTT
- ALT, bilirubin, LDH, ALK, phosphate, BUN, creatinine
- Hepatitis, HTLV1, HIV serology
- Quantitative serum immunoglobulins
- Beta-2-microglobulin
- Urinalysis
- Serum pregnancy test for patients of child bearing potential.This is a female who has not been postmenopausal for at least 12 consecutive months or who has not undergone previous surgical sterilization. Patients of child bearing potential must agree to use birth control while on study.
- Unilateral bone marrow aspiration and biopsy with cytogenetics, PCR for JH, bcl-2 (if follicular NHL), or bcl-1 (if mantle cell), FISH if clinically indicated, and flow cytometry
- Peripheral blood sample (10 cc EDTA) for adhesion molecules will be sent to Dr. Reuben's lab
- A sample of peripheral blood (10cc) will be drawn prior to treatment for PCR for JH, bcl-2 (if follicular) or bcl-1 (if mantle cell)
- CXR PA/lateral
- EKG, Echo or MUGA to assess cardiac function
- PFT to assess lung function
- CT scan of neck, chest, abdomen, pelvis, PET scan for disease staging.

Evaluation During Study

- Physical examination and toxicity evaluation at least weekly while the patient is hospitalized and as clinically indicated for outpatients
- CBC and platelets as indicated till completion of apheresis.
- ALT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes once a week till completion of apheresis.
- Absolute CD34 counts when WBC > 3.0 - 4.0/mm^3.
- Evaluation of peripheral blood will be evaluated for bcl-2 (if follicular NHL) or bcl-1 (if mantle cell). Evaluation of apheresis product for adhesion molecules will be sent to Dr Reuben's lab.

POST TREATMENT FOLLOW UP

- After autologous stem cell transplantation, CBC and platelets will be monitored until recovery.
- After recovery of counts patients will be followed up for incidence of disease relapse/progression for 1 year.

Statistical Considerations:

Design and Monitoring
Success will be defined in this trial as feasibility of mobilization with ofatumumab. We wish to insure that the mobilization rate is at least as great as with the standard of care (87%) at our institution, and we will monitor the mobilization rate after every 10 patients during the course of the trial. If there is reasonable evidence that it is less than 87%, we will terminate the trial early. At the end of the trial, we will estimate this rate with an exact 95% credible interval. Patients who drop out of the study before day 21 will be considered failures for this endpoint.

We wish to include at least 10 patients in each of the histologies mantle cell lymphoma (MCL), follicular cell lymphoma (FCL) and diffuse large-b-cell lymphoma (DLBCL) Based upon historical data on patients treated at M.D. Anderson Cancer Center, we expect 30% of patients in this patient population to have MCL, 30% to have FCL, and 40% to have DLBCL. With 50 patients, the probability of enrolling at least 10 patients in each histology will be greater than 90%. Also, since the study will include patients with different histologies who may have had different prior therapies (such as Hyper-CVAD, fludarabine-based regimens, radiation, etc., the suggested number of 50 patients may give us a sense of feasibility of this procedure within each category, in preparation for future larger studies.

We will use the method of Thall, Simon, and Estey (Thall PF, Simon RM and Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med. 1995;14:357-379.) to monitor both the mobilization rate and the rate of death within the first 28 days during the course of the trial. We will assume that the mobilization rate and death rate are independent and will assume a Beta(1.74, 0.26) prior distribution for the mobilization rate, which has a mean of 87%, %, and a Beta (0.2, 1.8) prior for the rate of death by day 28, which has a mean of 10%.

The following two decision criteria will be used: stop accrual if at any time during the course of the trial either A) or B) is met. We will evaluate these rules after each cohort of 10 patients has been evaluated at day 21/28. (It should be noted that the mobilization rate is assessed at day 21, while the safety endpoint is assessed at day 28.)

A) $\Pr\{\text{mobilization rate} \geq 87\% \mid \text{data from patients evaluated}\} < 0.025$

In other words, if at any time during the study we determine that there is less than a 2.5% chance that the mobilization rate is at least 87%, we will stop enrollment into the study. Stopping boundaries corresponding to this probability criterion are as follows: stop if:

[# of patients with mobilization/ # of patients evaluated at day 21]:

$\leq$ 5/10, 13/20, 21/30, or 29/40

B) $\Pr\{\text{Rate of death} \geq 10\% \mid \text{data from patients evaluated at day 28}\} > 0.95$

In other words, if at any time during the study we determine that there is greater than a 95% chance that the death rate is at least 10%, we will stop enrollment into the study. Stopping boundaries corresponding to this probability criterion are as follows: stop if:

[# of patients that have died by day 28/ # of patients evaluated at day 28]:

$\geq$ 4/10, 5/20, 7/30, or 8/40

The operating characteristics of these rules are shown in the following table:

Operating Characteristics for Feasibility and Safety Monitoring Rules:

True Mobilization Rate	True Death Rate	Probability of Stopping Early
87%	10%	9.6%
87%	5%	2.8%
87%	20%	62.7%
67%	10%	85.7%
97%	10%	7.3%
77%	10%	41.1%
87%	30%	95.6%

Additionally, to ensure patient safety, the rates that patients experience recovery of absolute neutrophil counts (ANC) and infection will be monitored by the study PI. For ANC count recovery, if any of the first five patients to enter the trial does not experience recovery of ANC counts by day 28, the trial will be temporarily halted pending review with the MDACC IRB. If the true rate of recovery is 99%, the probability of at least 1 patient failing to engraft within 28 days is less than 5%.

The rate of infection will be monitored closely by the study PI. If, in his clinical judgment, the infection rate is higher than acceptable, enrollment will be temporarily halted pending review with the MDACC IRB.

Where Will Participants Be Enrolled:

Only at MDACC

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

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

Estimated Accrual:

Total Accrual at MDACC: 50
Estimated monthly accrual at MDACC: 3

Accrual Comments:

Do you expect your target population to include non-english speaking participants? Yes

Please select expected languages of non-English speaking participants. (Select all that apply)
Expected languages of non-English speaking participants:

Spanish

Location of Treatment:

This protocol is performed on an Inpatient AND Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

Expected 4 days of hospitalization (standard practice for the chemotherapy to be used).

Return Visits: How often must participants come to MDACC?

Patients will return to MDA daily from time of discharge until completion of chemotherapy and then will have blood draws 2-3 times per week until the end of stem cell collection (per standard procedure). The apheresis will be done as an outpatient.

Home Care: Specify what, if any, treatment may be given at home.

N/A

Name of Person at MDACC Responsible for Data Management: Rosamar Valverde

Prior protocol at M. D. Anderson:
Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients?
Yes

Data Monitoring Committee:

Is treatment assignment randomized? No

Is this a blinded or double-blinded study? No

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

Please describe:
At the end of the trial, the mobilization rate and the death rate will be reported with 95% credible intervals.

The association between the mobilization rate and disease and demographic covariates of interest will be assessed with logistic regression.

The proportion of patients with the ability to purge malignant cells will be estimated with a 95% confidence interval. Additionally, logistic regression will be used to assess the association between this rate and disease and demographic characteristic of interest.

The time from transplant to the recovery of neutrophil counts will be estimated and graphed using the method of Kaplan and Meier. The median time to recovery will be estimated and compared with the standard of 13 days.

The proportion of patients with infection will be estimated with a 95% confidence interval, and episodes of infection will be summarized. Logistic regression will be used to model the association between the risk of infection and covariates of interest.

The number of apheresis procedures needed will be estimated, and linear regression will be used to assess the association between the number and characteristics of interest.

Total stem cell yield/patient body weight will be estimated, and the relationship between stem cell yield and characteristics of interest will be explored through linear regression.

The time to engraftment will be defined as the time from stem cell transplant to initial engraftment. Patients who do not engraft will be censored at day 28. The time to engraftment will be estimated using the Kaplan-Meier method, and Cox proportional hazards regression models will be used to assess the relationship with the degree of expression of various adhesion molecules.

For safety, descriptive statistics will be used to report the number and proportion of patients with adverse events by grade.

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Investigational New Drugs:

Does this protocol require an IND? Yes
Please list the IND holder and provide the IND number:

IND Holder: MDACC
IND Number: 111387

Investigational Device:

Is the Investigational Device approved by the FDA?	N/A
Is the Investigational Device being used in the manner approved by the FDA?	N/A
Has the Investigational Device been modified in a manner not approved by the FDA?	N/A

Name of Device:

Manufacturer:

What is the FDA Status of the Investigational Device?

Is the study being conducted under an Investigational Device Exemption (IDE)? No

IDE Holder:

IDE Number:

Risk Assessment:
Please answer the following questions regarding the Investigational Device.

Intended as an implant?	No
Purported or represented to be for use supporting or sustaining human life?	No
For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health?	No

You may attach sponsor documentation of the risk assessment:
NA

Will participant be charged for the Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? Yes

Sponsor or Supporter: Novartis
Type(s) of Support: Agent
Grant
Monitored by Sponsor or Sponsor Represenative (CRO)? Yes

Is this Protocol listed on any Federal Grant or Foundation Funding Application? No

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 stem cells? No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center? No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Other
Please provide the name of the test(s), the purpose of the test, and the performing laboratory identification and contact information.
A sample of peripheral blood (10 cc) will be evaluated for PCR for JH, bcl-2 (if follicular) or bcl-1 (if mantle cell). A sample of apheresis product (10 cc) will be sent to Dr. Reuben's lab for evaluation of dendritic cell population, natural killer cells, and adhesion molecules by 2-color flow cytometry. All leftover samples will be destroyed.

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? No