BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 0701

1. What is the rationale for conducting an allogeneic hematopoietic stem cell transplant trial in follicular non-Hodgkins lymphoma (NHL)?

Follicular NHL is the second most common type of non-Hodgkin's lymphoma with an incidence of ~15,000 new cases/year in the U.S. When treatment is indicated, most patients achieve a remission with initial chemotherapy. However, a continuous pattern of relapse typically follows resulting in progressively shorter remission duration. Patients with recurrent advanced follicular lymphoma have a median survival of 4-5 years.

At present, the optimal management of patients failing conventional therapy is unknown. Numerous options exist including either autologous hematopoietic stem cell transplantation (HSCT) or allogeneic HSCT. Several studies reporting the results of autologous HSCT have shown improved disease-free survival (DFS) but relapse remains the predominant cause of treatment failure. High dose chemo-radiotherapy with allogeneic HSCT has also been offered with the goal of harnessing a graft-versus-lymphoma effect and to circumvent the tumor cell contamination associated with autologous hematopoietic stem cell harvests. Lower relapse rates have been reported compared to autologous HSCT but the high treatment related mortality has offset any survival benefit.

Non-myeloablative (NMA) allogeneic HSCT incorporates a less intensive preparative regimen and relies primarily on the immunotherapeutic effects of the allograft to confer antilymphoma activity rather than the cytoreductive effects of high dose chemotherapy. The incorporation of lower doses of chemotherapy has resulted in lower treatment related mortality and additionally, the increasing use of NMA HSCT has extended eligibility of allogeneic HSCT to older patients who otherwise would not be eligible for a myeloablative allogeneic HSCT. Over the last decade, NMA HSCT has been increasingly offered to patients with various hematologic malignancies such as acute and chronic leukemia, lymphoma and multiple myeloma.

2. Why is the FCR (fludrarabine, cyclophosphamide, rituximab) regimen being utilized?

The most promising data published employing NMA HSCT in relapsed follicular NHL patients was initially reported by the M.D. Anderson Cancer Center in 2001 using the

FCR regimen in 20 patients. These results were recently updated with a total accrual of 47 patients. With a median follow-up of 34 months, the three year DFS, overall survival (OS) and risk of progression was 88%, 85% and 3%, respectively. Only 1 patient succumbed to treatment-related causes. These survival and relapse statistics unequivocally represent the most promising results reported to date for this specific patient population.

3. What is the purpose of validating results from a single institutional trial?

As mentioned above, the 3-year DFS of 88% is unequivocally the most encouraging results published to date in the treatment of recurrent follicular NHL. If these results can be replicated in a large multi-center trial, it would validate the above results, demonstrate the exportability of this regimen outside of M.D. Anderson, and potentially could become the standard regimen for patients with recurrent follicular NHL. No other transplant or non-transplant regimen to date has conferred such a high DFS and low disease progression rate.

4. How will the high dose rituximab be administered?

Rituximab can be safely administered using a "rapid infusion" protocol as published in the literature(Sehn et al. Blood 2007;109:4171; Salar et al. Eur J Haematol 2006;77:338; Provencio et al. Ann Oncol 2006;17:1027). Following these published guidelines, the high dose rituximab can be administered in ~3-4 hours in the outpatient setting. Centers will be provided with recommended administration guidelines.

5. What is the purpose of utilizing a high dose rituximab in the conditioning regimen?

Rituximab (RTX) is a chimeric monoclonal antibody recognizing CD20, an antigen expressed on all cells of B cell lineage including B cell non-Hodgkin's lymphoma. It has proven cytoreductive activity in all B cell lymphomas as both first line therapy and in the salvage setting. More recently, RTX has shown activity against both acute and chronic graft-Versus-Host Disease (GVHD). Another notable aspect of the above-mentioned M.D. Anderson results is the low incidence of acute GVHD, which has been partially attributed to use of high dose RTX. Thus, the purpose of RTX in this protocol is two fold: 1) upfront cytoreduction as part of the conditioning regimen and 2) potential reduction in incidence of GVHD.

6. Why is only one regimen (tacrolimus/methotrexate) allowed for graft-vs-host disease prophylaxis?

The combination of tacrolimus/methotrexate was the regimen utilized in the M.D. Anderson protocol. The Protocol Committee considered allowing additional regimens such as cyclosporine-based regimens. However, as the ultimate goal is to replicate the results from the original trial, the Committee felt that there should be minimal deviation from the original treatment schema.

7. Is your accrual goal of 65 patients feasible?

Yes. In looking at the CIBMTR data, the number of NMA allogeneic HSCT for patients with follicular NHL continues to increase. From 2000 to 2005, a total of 621 patients with recurrent follicular NHL underwent NMA HSCT in the U.S. with the numbers continuing to increase annually. In order to increase accrual, we have garnered upfront support and endorsement from the Cancer and Acute Leukemia Group B (CALGB) NCI cooperative group and we expect to receive the same endorsement and support from Southwest Oncology Group (SWOG) within the next few weeks. Therefore, this protocol will be supported by 3 major groups.

8. Are there novel correlative studies within this protocol?

Yes. We plan to measure serum rituximab levels at several time points after HSCT as data from early Phase I trials have demonstrated the persistence of RTX in the serum up to 1 year after administration with a direct correlation between RTX dose and duration of measurable serum levels. The incidence of relapse, acute GVHD and chronic GVHD will be compared between patients with detectable levels of serum rituximab and no detectable levels at the specified time-points. Therefore, we will use time-dependent covariates to examine the effect of rituximab levels for each outcome. The measurement of serum RTX levels and its impact or prediction on outcome has not been previously studied in the transplant setting.

9. Accrual Estimates – See separate summary of Accrual Estimates.

10. What are the recruitment strategies if applicable, and proposed plans for monitoring study accrual?

Core Clinical Centers, non-Core Centers, and Cooperative Group Centers (SWOG, and CALGB) will participate. Transplant centers will follow their local institutional practices for recruiting patients on research studies.

Patient information and educational materials explaining this study will be prepared by the NMDP Office of Patient Advocacy and made available to centers in paper form and on the Web.

Monthly accrual reports will be provided to the NIH. Additionally, recruitment reports based on the CIBMTR database will be provided every six months. The screening reports will summarize reasons for non-enrollment and reasons for ineligibility.

11. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used for all BMT CTN supplemental forms. Data are transmitted encrypted using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online

missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference and training of clinical research associates (CRAs).

Data collected on CIBMTR Initial and Follow-up Report Forms will be transferred electronically from the CIBMTR to EMMES on a regular basis. Any data relevant to real-time monitoring of safety or efficacy endpoints will be collected on BMT CTN supplemental forms, e.g. deaths.

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in each protocol.

12. What is the monitoring and overall coordination of protocol management (e.g. brief summary of plans to run the study – initiation, coordination, data collection, and monitoring)?

A protocol coordinator is assigned to each BMT CTN protocol. The protocol coordinator is responsible for the daily operational needs of the study and of the participating transplant centers. The protocol coordinator oversees enrollment and data collection issues and is in regular communication with CRAs at participating transplant centers. The protocol coordinator also works closely with the protocol officer with respect to adverse event reporting and to medically related protocol questions.

A form submission schedule is developed for each BMT CTN protocol and is included in these materials. A visit schedule will be provided to the transplant centers for every enrolled patient. This schedule will detail the dates of all expected visits and list of forms and/or samples required at each visit.

Initiation site visits will be conducted for all participating centers. These visits will either be in-person visits to the centers or be held via conference call with all transplant center personnel involved with this protocol.

DCC staff, including at a minimum the protocol coordinator, will conduct periodic monitoring visits to the participating clinical centers and laboratories. The primary purpose of these visits is to conduct data audits. Other activities include those required to enhance data quality, ensure study integrity, satisfy regulatory requirements, and evaluate site performance. Site visits will occur at variable frequency throughout the course of the studies, depending primarily upon the stage of the study, site performance, and sponsoring agency requirements.

Unexpected serious adverse experiences will be reported according to BMT CTN guidelines. The protocol officer will review all unexpected serious adverse experiences.

Expected transplant-related toxicities will be collected on each patient using the calendar-driven reporting system that has been previously reviewed and approved by the DSMB. There is an interim statistical monitoring plan for efficacy and safety endpoints. The protocol statistician or other DCC statistical staff will ensure that programs are in place to conduct the interim monitoring in accordance with the statistical analysis plans in each protocol.

13. Are there any specific study training plans necessary to accomplish the research goals (e.g. workshops, study certification)?

CRAs will be certified for data submission by the DCC after participating in an in-person meeting or in a training session conference call with the protocol coordinator. No other certifications or workshops will be required for this study.