BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 0301

1. Why conduct a transplant trial in severe aplastic anemia (SAA)?

Severe aplastic anemia is relatively uncommon but life-threatening condition. While immunosuppressive therapy can lead to improvement in blood counts and reduced transfusion requirements, allogeneic bone marrow transplantation is the only curative option. Most patients do not have an HLA-identical sibling donor, and therefore will need a matched unrelated donor. However, there is considerable disagreement on what is the best approach to allografting in these patients. A prospective transplant trial is the most logical and effective way to optimize their management and improve their long-term outcome.

2. What is the current "standard of care" for SAA patients undergoing a matched unrelated donor marrow transplant?

There is no uniformly accepted "standard of care" with regard to the preparative regimen to be employed in these patients. A variety of preparative regimens have been employed, although results have frequently been disappointing. Based on the results published by Deeg J et al (Biol Blood Marrow Transpl 7: 208-215, 2001) and recently updated (Deeg J; personal communication, 2004), a preparative regimen with high-dose cyclophosphamide, antithymocyte globulin, and low-dose total body radiation would seem to provide the best long-term engraftment and survival results. However, it was still associated with considerable transplant-related morbidity and mortality.

3. Why introduce fludarabine in the preparative regimen for transplantation?

Fludarabine is a powerful immunosuppressant agent and has few extrahematological side effects. It does not cause mucositis or significant toxicity or damage to heart, lung, kidneys or the gastrointestinal tract. Fludarabine-based preparative regimens are increasingly employed in bone marrow transplantation for other hematologic disease such as leukemia or lymphoma.

4. Why attempt to reduce the cyclophosphamide dosage in the preparative regimen?

High-dose cyclophosphamide, while effective, has substantial toxicities such as mucositis, hemorrhagic cystitis, liver toxicity and cardiomyopathy. These toxicities are

dose-dependent and can be severe or life-threatening. Antithymocyte globulin is usually associated with fewer severe or life-threatening toxicities. Low-dose total body radiation, while not without potentially serious complications such as interstitial pneumonitis, is felt to be essential to ensure engraftment.

5. Why choose two-year survival as the primary endpoint?

Two-year survival was chosen as an endpoint as earlier time points would likely not allow us to capture the impact of chronic graft-versus-host disease (GVHD) and late complications on the outcome of these patients.

6. Is the accrual goal feasible?

Yes. We carefully analyzed the NMDP data on past transplant activity for SAA from both Core and non-Core centers and supplemented this with a separate survey of Core Centers to determine willingness to participate. (See separate summary of Accrual Estimates.) It should be noted that the number of patients receiving transplants for SAA has trended upward in the past few years.

7. Is there a need for a multi-center network to meet the objectives?

Yes. SAA is an uncommon referral diagnosis for transplant centers. Its incidence in Europe and North America is only around two cases per million population per year. No single center treats sufficient numbers of patients to complete this study in a reasonable timeframe. For the same reason, randomization is not a feasible strategy when conducting a prospective study in these patients.

8. Why does the protocol require three graft failures in the first six patients (50%) to disqualify a dose if the acceptable graft failure probability threshold is 0.20?

Very briefly, the stopping rule must have high power to select the optimal dose among acceptable doses, and to stop early when there is no acceptable dose. Below we show why our "3/6" guideline accomplishes this, but a two graft failures in the first six patients ("2/6") guideline does not.

In the aplastic anemia study, the dose finding algorithm searches for the optimal dose among doses with acceptable graft failure ($\leq 20\%$) and toxicity ($\leq 40\%$) rates. Consider scenarios A, B and C in Tables 1 and 2 below. The dose levels listed in Tables 1 and 2 are described in Table 5.3 from the protocol. The first cohort of patients is put on dose 3.

For Scenario A, dose 3 (the highest dose) is the optimal dose with a 10% graft failure rate. The loss of trial power going from the 3/6 rule to the 2/6 rule is seen in the increase

in stopping probabilities from 3% to 16%, the decrease in selecting an acceptable dose from 95% to 83%, and the decrease in selecting the optimal dose from 79% to 74%.

For Scenario B, dose 3 is the optimal dose with a 15% graft failure rate; there are no other acceptable doses. The loss of trial power going from the 3/6 rule to the 2/6 rule is seen in the increase in stopping probabilities from 15% to 40% and the decrease in selecting the optimal dose from 79% to 57%.

For Scenario C, dose 3 has a 30% graft failure rate, and there is no acceptable dose. With the 3/6 rule, the stopping probability is 92%, which is quite ample, but improves to 98% with the 2/6 rule.

In conclusion, to maintain reasonable power to select the optimal dose while preserving power to stop early when there is not acceptable dose, the 3/6 rule is acceptable, but the 2/6 is not.

Note that by using a stopping rule of three graft failures in the first six subjects, we are NOT "targeting" or "permitting" a graft failure rate of 50%. As shown in Scenario C, a graft failure rate of 30% or higher will result in trial closure over 92% of the time.

Table 1: Hypothetical Settings used in the Simulation Study for the CY Dose Finding Scheme

	CY Dose Level **Probability of Toxicity or Early Death / Probability of Engraftment**			
Scenario	**0**	**1**	**2**	**3**
A	.30/.60	.30/.70	**.30/.80**	***.30/.90***
B	.05/.40	.10/.55	.15/.70	***.20/.85***
C	.05/.25	.10/.40	.15/.55	*.20/.70*

Table 2: Statistical Properties of the CY Dose Finding Scheme: 2/6 Graft Failure Rule Versus 3/6 Graft Failure Rule

	Probability of Each Dose Being the Final Selection					Average Number of Patients Treated at Each Dose			
Scenario	**Stop***	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
A: 2/6	**.163**	.000	.006	**.095**	***.737***	1	4	13	50
A: 3/6	**.034**	.001	.014	**.157**	***.793***	4	7	18	47
B: 2/6	**.404**	.000	.000	.022	***.574***	0	1	8	46
B: 3/6	**.150**	.000	.002	.059	***.788***	1	5	14	51
C: 2/6	**.984**	.000	.000	.000	.015	0	0	2	13
C: 3/6	**.923**	.000	.000	.001	.077	0	2	6	24

*Stops and fails to find a dose.

For Scenario A, doses 2 and 3 are acceptable while dose 3 is optimal. For Scenario B, only dose 3 is acceptable, hence optimal. There are no acceptable doses in Scenario C.

9. There is a 42 day waiting period between the time a cohort enrolls its sixth (final) patient and the cohort has complete follow-up for subsequent dose selection. If an eligible patient was identified during that waiting time, will that patient not be enrolled or will the patient be enrolled at the same dose as the previously-enrolled patient and then not use the previously-enrolled patient's data for dose selection?

It is highly unlikely that an eligible patient will be identified during the waiting time between cohorts ***and*** the dose the patient should receive is not determined from the current trial follow-up. In this highly unlikely event, the waiting time should be brief because the previous patient should be finishing the 42 day follow-up. Every effort will be made to maintain the eligible patient until the previous patient's 42 day follow-up is completed.

10. Accrual estimates – See separate summary of Accrual Estimates.

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

Core Clinical Centers and non-Core Centers 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.

12. 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.

13. 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)?

An investigators meeting will be conducted for this protocol at the 2005 Tandem BMT Meetings. Training meetings for CRAs will be regularly conducted in conjunction with either NMDP and/or CIBMTR annual meetings and by teleconference.

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.

14. 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.