BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs FOR BMT CTN PROTOCOL 0801

Study Question and Study Population

1. What is the current "standard of care" for chronic GVHD therapy?

The standard initial treatment (IST) for cGVHD is prednisone +/- calcineurin inhibitor (CNI). Prednisone dosing begins at ≤1 mg/kg/day until such time that acute inflammatory manifestations are controlled, after which dosing is transitioned to a less toxic every-other-day regimen for longer term therapy.

2. Why conduct an early intervention therapy trial for chronic GVHD?

The goal of cGVHD treatment is to control symptoms, prevent permanent organ damage, and minimize treatment toxicity until tolerance is achieved. This trial is testing whether alterations in early treatment for high risk or inadequately responding standard risk patients improves cGVHD control, facilitates tolerance and prevents the need for additional agents. Consensus in the field is that greater effort should be devoted to preventing steroid-refractory cGVHD through early treatment trials.

3. Why not restrict the eligibility to newly diagnosed chronic GVHD?

All clinical trials in cGVHD have historically been hampered by slow accrual. To a large extent this can be explained by overly stringent eligibility criteria and clinical trial requirements that are incompatible with mainstream clinical care practices. The 0801 study encourages physicians to enroll patients with newly diagnosed high-risk cGVHD but also allows the common practice of short term "testing" of prednisone treatment. The 0801 study will accept patients that have received up to 12 weeks of standard IST and up to one additional agent started with initial therapy. The Writing Group of cGVHD experts noted that 12 weeks is a relatively short period of time compared to the median 2 to 3 year duration of IST for cGVHD depending on stem cell source, and that these inclusion criteria should optimize accrual yet avoid inappropriate enrollment of patients with advanced cGVHD which has become refractory to prolonged prednisone and multiple steroid-sparing agents.

4. Why include all graft sources, GVHD prophylaxis regimens etc? Should the population be more homogeneous?

All graft sources are included in order to maximize accrual and so that study results may be representative of the entire spectrum of cGVHD patients. It is anticipated that randomization should result in even distribution of transplant-related characteristics.

Choice of Study Intervention

5. Why a 3-drug comparator arm and not a 2-drug or even prednisone-only comparator arm?

All patients on the trial are high risk by virtue of their presenting characteristics or their inadequate response to prednisone-based treatment. Many of these patients will also have a CNI in their initial treatment regimen. Addition of another agent is required for those with an inadequate response to initial treatment, resulting in a 3-drug comparator arm (prednisone + CNI + sirolimus). For patients at high risk, it is reasonable to add sirolimus to the initial treatment regimen since responses to prednisone+CNI are known to be inadequate.

6. Why test sirolimus ± extracoroporeal photopheresis as the experimental therapies over other agents for which preliminary data exist?

The study team reviewed the available agents for which published efficacy and toxicity data exist. The leading candidates included: mycophenolate mofetil, extracorporeal photopheresis (ECP), sirolimus, pentostatin and rituximab. Mycophenolate mofetil was not beneficial in a randomized, placebo-controlled trial of initial therapy and was eliminated from consideration. The Writing Group felt that the infection risks associated with pentostatin lowered the enthusiasm for its early use in cGVHD. In addition, there was only one Phase II study that involved ~50 patients. Among the three remaining agents, there was significant interest in testing the concept that enhancing regulatory T cells could facilitate graft tolerance through sirolimus and ECP. Data from Phase II trials in patients with steroid-refractory cGVHD suggest ECP (n> 250) and sirolimus (n~140) are beneficial. Laboratory data suggest that ECP and sirolimus expand T_{regs}.

7. Why not test ECP without sirolimus as one of the experimental arms?

The testing of ECP alone would certainly be of academic interest. However, all Phase II testing of ECP in cGVHD has done so in the context of baseline therapy with glucocorticoids and a CNI (± mycophenolate mofetil in the most recent trial published by Flowers et al). ECP is believed to work slowly, necessitating addition of another agent anyways. Sirolimus is an ideal candidate to combine with ECP because its effects on T_{regs} might be complimentary (or even synergistic) with ECP, and sirolimus also has anti-B cell activity which might be of value in maintaining daily control of GVHD as ECP is tapered.

8. Why remove the calcineurin-inhibitor from the experimental arms?

Laboratory and clinical data suggest that CNIs may interfere with induction of tolerance. In relevant murine transplant models cyclosporine significantly reduced T_{reg} function in vivo as assessed by increased proliferation of T_{conv}, GVHD severity, and reduced survival. The reduced suppressor function of cyclosporine-exposed T_{regs} was IL-2 dependent and correlated with a reduced number of *FOXP3*+ T cells in vitro and in vivo, suggesting the critical importance of calcineurin-dependent IL-2 production. Both thymic generation and peripheral preservation of *FOXP3* T_{regs} appear to be negatively regulated by cyclosporine and facilitated by sirolimus.

A subset analysis from one randomized study suggested that survival was worse when progressive onset cGVHD was treated with cyclosporine plus prednisone compared to prednisone alone.

9. What are the potential risks of removing a calcineurin-inhibitor?

Data from a randomized primary therapy study in cGVHD [Koc et al. Blood 2002] and recent empirical data from four centers suggest that it is safe to discontinue a CNI during the treatment of cGVHD, especially if another agent is added concurrently. Previous randomized trials had also suggested that the incidence of cGVHD was not affected by early discontinuation of cyclosporine in patients who did not have acute GVHD on Day 60 after transplantation or by prolongation of cyclosporine in patients who did not have cGVHD on Day 80 after transplantation. A survey of 4 large institutions (30 patients) found that major flares of acute inflammatory GVHD manifestations were not observed when CNIs were discontinued abruptly or after a brief taper.

10. Why not choose therapies that target B cells based on recent reports that abnormal B cell homeostasis is involved in the pathophysiology of chronic GVHD?

During the earlier conference calls the enthusiasm was lower among cGVHD experts for targeting B cells with rituximab than for approaches which might modulate T_{regs}. This sentiment was even expressed by one center that had published their results of rituximab therapy for steroid-refractory cGVHD. This same center expressed a particular enthusiasm for evaluating ECP. Published aggregate Phase II data for rituximab also involved a smaller number of patients than for sirolimus or ECP. Lastly, sirolimus is not devoid of B cell effects as it has been reported that sirolimus inhibits B-cell proliferation and immunoglobulin production, and can also induce B cell apoptosis.

Choice of Study Design

11. Why were two parallel 2-arm studies chosen rather than a single 3 arm study?

This issue was carefully discussed and it was felt that a single 3-arm study was not feasible. Based on the experience in the BMT CTN 0402 study (4-arm randomized study of acute GVHD treatment), it is difficult to explain a study with more than 2 arms and engender patient and physician enthusiasm. There are also some centers that strongly wish to have an ECP experimental arm and others that do not for a variety of reasons. Thus, each center will participate in only one Phase II study at a time.

12. Why a Phase II/III rather than a Phase II?

The study was initially designed as a Phase II but was modified to an adaptive Phase II/III on the advice of the BMT CTN Steering Committee. This approach results in less overall study time (since the Phase III is already written and approved), more efficient use of enrolled patients (since 100 patients from the winning Phase II trial will be included in the Phase III), and avoids disruption in center enthusiasm as the Phase II portion is closed the Phase III is activated.

In the event that neither experimental arm performs better than the comparator arm the 0801 trial will end at Phase II and no further effort will be wasted pursuing a Phase III.

13. Why choose complete + partial response rate at 6 months for the primary endpoint of the Phase II and durable complete response at 2 years for the Phase III?

After lengthy consideration, the 0801 Writing Group selected the 6 month CR+PR rate as the primary endpoint for the Phase II because it is achievable within a realistic timeframe and is appropriate for early phase testing. The NIH consensus conference response criteria were not felt to be validated yet for clinical trial use, although the measures will be collected during this study. More robust endpoints like survival, or discontinuation of all systemic IST, are incongruent with the goal of timely completion of a multicenter study in an orphan disease like cGVHD.

14. Why not use addition of rescue therapy as a primary endpoint?

The addition of rescue therapy might be considered slightly more objective as a response endpoint than CR+PR because it reflects the strength of a physician's determination that a patient is failing therapy. However, the Writing Group chose the fixed early primary endpoint at 6 months because it is achievable in a more realistic timeframe, and we had preliminary data on this endpoint available. Treatment failure (addition of rescue therapy) is a secondary endpoint.

15. Why is there no blinding of study therapies?

The blinding of study therapies is not feasible from practical and fiscal standpoints. In order to blind study subjects and physicians to the ECP, the patient must either undergo recurrent peripheral venous cannulation or central venous access must be established. Subjects would also have to undergo sham ECP procedures for the duration of therapy. Such activities would be costly and ethically questionable given the lack of medical necessity.

The comparator arm involves three different pills (P+SRL+CNI), whereas the treatment arms involve two pills (P+SRL). It would be costly to obtain the necessary placebo formulations to make blinding possible. The non-overlapping toxicities of CNI-based and CNI-free regimens and the necessary monitoring of CNI and SRL drug levels would also make it impossible to blind physicians.

16. Why is there no blinding of response measurement?

The assessment of cGVHD requires a level of expertise/experience and, as historically been the case, the very nature of longitudinal follow-up of patients with cGVHD is an integral part of an individual physician's response assessment. The Writing Group recognized that it was impractical to either train blinded reviewers, or have centers designate an individual(s) who was not involved in patient care, for the purpose of achieving blinded assessments, particularly at smaller sites with fewer personnel. The historical benchmark for response was also based on non-blinded assessments. A secondary analysis will evaluate the new NIH tools aimed at defining more objectively measuring CRs and PRs.

17. Should the steroid taper be more strictly prescribed?

The 0801 Writing Group believes that the steroid taper should be at the discretion of the managing physician to reflect "real-world" practices. A protocol prescribed taper would be impossible to enforce and would discourage participation in the trial. A major secondary

endpoint is to measure the cumulative reduction in prednisone dose which will be considered in conjunction with the primary endpoint when evaluating the overall clinical benefit of a "winning" study arm that has the best response rate.

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

19. 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.

20. 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.

21. What is the monitoring and overall coordination of protocol management (eg. 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.

22. Are there any specific study training plans necessary to accomplish the research goals (eg. 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.

Each study site will be provided with copies of the DVD: "Measuring Therapeutic Response in Chronic GVHD Trials: An Instructional Manual" Editors: S.A. Mitchell and S.Z. Pavletic. This DVD provides visual instruction for using the NIH response assessment tools using actual patients. In addition, in-person training sessions will be held at the annual Tandem meeting to provide additional training opportunities.