University of Wisconsin Blood and Bone Marrow Transplant
Treatment Management Plan

Allogeneic Reduced Intensity Transplant with
Rituxan, Fludarabine and Cyclophosphamide Conditioning Regimen and
Tacrolimus and Methotrexate Immunosuppression

version dated 2/4/08
I. Allogeneic BMT Background

Allogeneic bone marrow transplantation (BMT) became feasible in the 1960s after elucidation of the Human Leukocyte Antigen (HLA) complex. Since then, the therapy has evolved into an effective therapy for many hematologic disorders. Otherwise incurable malignancies are frequently cured by this approach, with the likelihood of cure ranging from 10% to 85%, depending on the disease and disease-status. The treatment strategy incorporates very large doses of chemotherapy and often radiation to eliminate cancer cells and to immunosuppress the recipient enough to allow engraftment of donor cells. Donor cells give rise to hematopoiesis within two to three weeks, rescuing the patient from the effects of high dose therapy. In the ideal circumstance, immune recovery and recipient-specific tolerance occurs over the following 6-18 months, and the patient is cured of his underlying hematologic disorder, off of immunosuppression, with a functionally intact donor-derived immune system. However, complications of the process are common and include fatal organ damage from the effects of high dose chemotherapy, infection, hemorrhage, and, in particular, graft-versus-host-disease. A realistic estimate of transplant-related mortality in the standard HLA-matched sibling setting is approximately 25%. The risk of treatment related mortality thus limits the success of the approach in younger patients and certainly precludes its use in older patients. Thus, new strategies in transplantation are needed.

Shifting emphasis in BMT toward adoptive immunotheraphy

With the growing understanding that much of the curative potential of allogeneic BMT is from an immune anti-tumor effect of donor cells called graft-versus-leukemia (GVL), several investigators have begun to investigate a new strategy which shifts emphasis from high dose chemotherapy to donor-derived immune-mediated anti-tumor therapy. In this approach, patients receive preparative regimens which, while having some anti-tumor activity, are mainly designed to be immunosuppressive enough to allow engraftment of donor stem cells and lymphocytes. Engrafted lymphocytes may then mediate a GVL effect; if the GVL effect of the initial transplant is not sufficient, then additional lymphocytes may be infused (achievement of engraftment allows additional lymphocytes to "take" in the recipient without any additional conditioning of the recipient required). The lower intensity of the preparative regimen should lessen the overall toxicity of allogeneic BMT by exposing the patient to much less chemoradiotherapy. In addition, less intensive preparative regimens may be associated with less GVHD, as much evidence suggests that high dose therapy contributes to the syndrome of GVHD by causing tissue damage, leading to a cytokine milieu which enhances activation of GVH effector cells. Thus, such a transplant approach may allow the safer use of allogeneic transplants in standard populations and may allow extension of allogeneic transplantation to patients who could not withstand standard transplants because of age or co-morbid illnesses.
This protocol investigates a non-myeloablative transplant approach, using cyclophosphamide and fludarabine as a way of allowing engraftment of allogeneic cells which then may mediate anti-tumor effects.

II. Patient selection

1. Diagnosis of:

2. Age $\geq 10$ and $< 70$

3. Karnofsky performance score $> 80$

4. No evidence of active infection

5. HIV nonreactive

6. No active hepatitis B

7. No active hepatitis C

8. Recipients must have a pretransplant multiorgan assessment prior to transplant with the following:
   
   8.1 Cardiac: resting ejection fraction of $> 45\%$ as demonstrated by echocardiogram or MUGA scan; without angina or uncompensated congestive heart failure requiring treatment of myocardial infarction within the past year
   
   8.2 Pulmonary: DLCO, corrected for hemoglobin of $> 50\%$ and/or an FEV1 of $> 50\%$
   
   8.3 Renal: serum creatinine of $< 2.0$ mg/dL
   
   8.4 Hepatic: total bilirubin $< 2.5$ mg/dL; AST $< 2.5$ times upper limit of normal

9. HLA matched related donor OR one antigen mismatched related donor OR fully matched unrelated donor.

10. Not currently smoking.

11. Diabetes must be controlled.

12. Psychiatric illness other than depression may make patient ineligible.
13. Must be not be HIV positive, have chronic active hepatitis B or C.

14. Must not be currently a smoker.

III. Treatment regimen

1. Conditioning Regimen
   Day 0 is defined as the day of allogeneic stem cell infusion.

   Regimen may be administered in the outpatient clinic or hospital, depending on clinical circumstances.

   Hydration. Patients deemed at risk for tumor lysis syndrome should receive adequate hydration (NS at least 150ml/m²/h) beginning on the first day of chemotherapy (day –6) and allopurinol 300mg/d from day –6 to day –1).

   Rituximab 375 mg/m² will be given intravenously according to standard infusion guidelines on day –13, –6, +1 and +8. Rituximab dose will be based on ACTUAL body weight. NOTE: Patients with Hodgkin’s disease WILL receive rituximab.

   Fludarabine 30 mg/m² in NS intravenously on days -6, -5, -4, for a total of 3 doses. Fludarabine will be dosed according to ACTUAL body weight.

   Cyclophosphamide 750 mg/m² intravenously on days -6, -5, -4 for a total of 3 doses. Cyclophosphamide will be dosed according to ACTUAL body weight. Days –3, -2 and -1 are rest days.

2. Immunosuppression regimen

   Tacrolimus: 0.09 mg/kg/day PO, based on actual body weight, will start on Day -2 and continue until Day +90 post HSCT. Tacrolimus will be given orally in a twice daily divided dose. Tacrolimus dosing should be based on actual body weight. Doses should be adjusted to maintain whole blood “trough” levels at 5-15 ng/mL. Tapering of tacrolimus doses should commence starting at Day +90 post HSCT to be completely discontinued by day +180 post HSCT unless GVHD develops. An equivalent dose of IV tacrolimus may be used.

   Patients with severe intolerance to tacrolimus may be placed on cyclosporine at a starting dose of 5 mg/kg bid PO based on actual body weight. An equivalent dose of IV cyclosporine may be used. Doses should be adjusted to maintain whole blood “trough” levels that target 500 ng/mL (upper end of therapeutic range) during the first month. Dose reductions should only be made if CSA
toxicity is present or whole blood levels exceed 600 ng/mL in the absence of toxicity. Further CSA determinations should be performed weekly until CSA is stopped unless high levels are detected (i.e. >600 ng/mL) or toxicity is suspected in which case more frequent monitoring will be performed as clinically indicated. Dose reductions for high levels without toxicity should be conservative (e.g. 25%) to avoid inadequate immunosuppression. After day +28 the CSA level is to be kept within 200-400 ng/mL until the Day +90 taper is initiated.

Methotrexate: 15 mg/m² IVP will be administered on Day +1 post HSCT. Methotrexate 10 mg/m2 IVP will be administered on days +3, +6 and +11 post HSCT. In the event of renal impairment, dose modifications should be made as indicated.

3. Allogeneic Stem Cell Infusion
The donor PBSC will be infused on day 0.

IV. Supportive care.

Patients will be provided supportive care, including infection prophylaxis and transfusion support, as per UW Hospital and Clinics Blood and Marrow Transplant Clinical Standard Operating procedures or as clinically indicated.

V. Follow up schedule

Upon discharge from the hospital, patients will return to clinic as clinically indicated but will typically return to clinic weekly for the first 100 days post transplant.

References


Appendix A

Allogeneic Reduced Intensity Transplant with Rituxan, Fludarabine and Cyclophosphamide Conditioning Regimen and Tacrolimus and Methotrexate Immunosuppression

Treatment Schema

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### Follow-up schedule

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1. Chem panel to include electrolytes, magnesium, calcium, phosphate, cholesterol, uric acid, BUN, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, LD, GGT
2. Infectious disease testing to include HIV 1 and 2 antibody, HTLV antibody, Hepatitis B panel to include Hepatitis B surface antigen, core antibody and surface antibody, Hepatitis C total antibody (if positive, hepatitis C RNA quantitation), syphilis by RPR, Toxoplasma IgM and IgG, EBV-VCA IgM and IgG, CMV IgG antibody (if positive CMV DNA capture)
3. Performed on peripheral blood. Pretransplant chimerism study requires a 5 ml lavender top tube sent to the UWHC HLA lab for STR analysis. Post transplant chimerism requires a 10 ml lavender top tube for sorted chimerism.
4. PFT’s are indicated in those patients with a history of GVHD.
5. Total CD20, CD3, CD4, CD8 on peripheral blood.