Chapter 8: Acute GvHD Prophylaxis

Purpose: Acute GvHD often occurs in patients who have received allogeneic stem cell transplants. This serves as a guide to treatment for such patients. Individual treatment plans may vary.

Scope: These guidelines outline the routine GvHD prophylaxis for patients who have received allogeneic hematopoietic stem cell transplantation at the University of Kentucky Markey Cancer Center.

I. Background
II. Factors that Influence Occurrence and Severity
III. Prevention of Acute GVHD
IV. Primary Prophylaxis
V. Authors
VI. References
VII. See Also
I. Background
A. Acute graft versus host disease (AGVHD) is a major cause of morbidity and mortality in patients undergoing allogeneic transplantation.
B. Measures that effectively prevent or treat acute graft versus host disease have a significant impact in improving survival in allogeneic recipients.

II. Factors that Influence Occurrence and Severity
A. Donor-Host Factors
   1. The incidence of GVHD increases with unrelated matched donor transplants compared with related matched transplants.
   2. With increasing HLA disparity, the incidence and severity of GVHD increases.
   3. Sex mismatching and increasing age of both donor (really?) and recipient increase the frequency of GVHD.
B. Stem-Cell Source
   1. Allogeneic peripheral blood stem cells (PBSC) may increase the incidence of chronic GVHD and prolong follow-up.
C. Immune Modulation
   1. The efficacy of post-transplant immunosuppressive prophylaxis affects the development of GVHD.
D. High-Dose Chemotherapy and Radiation Therapy
   1. After high-dose chemotherapy, levels of circulating cytokines increase; this is known as a cytokine storm. These cytokines may increase the ability of graft immune cells to recognize host antigens.
   2. High-dose chemotherapy can also lead to localized tissue damage, exposing cryptic antigens in certain organs (e.g., skin, liver, gut).
   3. Conditioning regimens including total-body irradiation are associated with an increased incidence and severity of GVHD compared with chemotherapy alone.

III. Prevention of Acute GVHD
A. Some of the strategies used to reduce the risk of developing aGVHD may include the following:
   1. Intensive prophylaxis with immunosuppressive drugs is standard practice for all patients undergoing allogeneic transplantation.
   2. Standard drugs in use include, but are not limited to, cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil, corticosteroids or antithymocyte globulin (ATG) & Alemtuzumab (Campath).
   3. Acute GVHD Prophylaxis for adults and children
      a) Always check protocol for specifics.
      b) Doses are, unless otherwise noted, calculated on corrected ideal body weight.

IV. Primary Prophylaxis
A. Recipients of non-T cell depleted, HLA-matched (at least 9 major antigens) sibling donor bone marrow (BM) or peripheral blood stem cells (PBSC) 6
   1. Methotrexate (MTX) (also known as Rheumatrex or amethopterin)
      a) Always check protocol for specifics.
      b) Give 1st dose 24 hours after stem cell infusion. See Table 1: Methotrexate (MTX) Dosing for GvHD Prophylaxis, on page 5.
      c) Serum creatinine must be checked prior to each dose. MTX will be held until the attending physician issues written approval. See Table 2: Methotrexate (MTX) Dose Modification for Renal Insufficiency, on page 5.
      d) Dose will be based on actual body weight.
e) Methotrexate will not be administered to recipients of non-T cell depleted, HLA-matched (at least 5 major antigens) sibling donor bone marrow (BM) or peripheral blood stem cells (PBSC) who have received reduced intensity preparative regimen with anti-thymocyte globulin.

2. Tacrolimus (also known as Prograf, FK506 or FK)
   a) Always check protocol for specifics.
   b) Give Tacrolimus 0.03 mg/kg CIVI (continuous IV infusion) starting day –1 for 180 days. Tacrolimus dose will be based on ideal body weight (IBW).
   c) When changed from intravenous (IV) to oral administration (PO), a total dose 3 times the IV dose will be given in divided doses twice daily (BID).
   d) Levels will be checked at least twice weekly during the hospital stay and then weekly until day +100. Then levels will be checked every 2-4 weeks until Tacrolimus is stopped. See Table 3: Tacrolimus Dosing for GvHD Prophylaxis, on page 5.
   e) The Tacrolimus level target is 5-10 ng/mL assuming that the patient’s renal function, blood pressure and other side–effects permit. See Table 4: Tacrolimus Dose Modification for Renal Insufficiency, on page 5.

B. Recipients of unrelated, non-T cell depleted, HLA-matched (at least 9 major antigens) bone marrow (BM) or peripheral blood stem cells (PBSC) may be treated with methotrexate and tacrolimus as above or with Alemtuzumab (Campath).
   1. Always check protocol for specifics.
   2. Alemtuzumab (also known as Campath, MabCampath, or Campath-1H)
      a) Administer Campath as 20 mg in 250 ml normal saline over a period of 3 hours. This dosage should be administered for 3 days in a row, from day -7 through day -5. See Table 5: Campath Dosing for GvHD Prophylaxis, on page 5.
      b) Patients should be euvolemic prior to treatment. Avoid co-administration with other agents that are associated with allergic reactions.
      c) Pre-medicate patients with Benadryl 50 mg orally and Tylenol 650 mg orally prior to dosing. Monitor patient closely for infusion-related adverse events.
      d) Careful monitoring of blood pressure is recommended, especially in patients with a history of ischemic heart disease and in patients on antihypertensive medications.
      e) Give 200 mg of hydrocortisone IV on the first day of administration, 100 mg on the second day and then 50 mg on subsequent days. Monitor vital signs every 30 minutes. Infusion time is 3 hours.
      f) Administer Methotrexate (Table 1: Methotrexate (MTX) Dosing for GvHD Prophylaxis; and Table 2: Methotrexate (MTX) Dose Modification for Renal Insufficiency). Administer first 24 hours after the completion of the stem cell infusion.
      g) Administer Tacrolimus as detailed above. See Table 3: Tacrolimus Dosing for GvHD Prophylaxis and Table 4: Tacrolimus Dose Modification for Renal Insufficiency, on page 5.

C. Recipients of unrelated, T-cell depleted, HLA-matched (at least 9 major antigens) bone marrow (BM) or peripheral blood stem cells (PBSC) may be treated with methotrexate and tacrolimus as above, or alternatively with Cyclosporine A.
   1. Always check protocol for specifics.
   2. Cyclosporine A (CSA) (also known as Sandimmune or Neoral)
      a) Give CSA 3 mg/kg by continuous IV starting day –2 for 180 days. See Table 6: Cyclosporine A (CSA) Dosing, on page 5.
      b) Levels will be checked at least twice weekly during the hospital stay and then weekly until day +100. Then levels will be checked every 2-4 weeks until cyclosporine A is stopped.
      c) The cyclosporine A level target is 150-400 ng/mL assuming that the patient’s renal function, blood pressure and other side–effects permit.
3. In lieu of tacrolimus and methotrexate, recipients of related or unrelated, T-cell or non-T cell depleted, HLA-matched (at least 9 major antigens) Bone marrow (BM) or peripheral blood stem cells (PBSC) may be treated with cyclosporine A (as above) with methylprednisolone (also known as Medrol, Solu-Medrol, Depo-Medrol) 30 mg/m² via IV or orally for 14 days starting D +5, then decrease 10% per week as tolerated.

D. Recipients of related, non-T cell depleted, partially HLA-matched (< 9 major antigens) BM or PB stem cells may be treated with Campath, methotrexate and tacrolimus as described above. Always check protocol for specifics.

E. Recipients of non-T cell depleted, HLA-matched (at least 9 major antigens) sibling donor BM or PB stem cells who receive non-myeloablative conditioning,

1. Always check protocol for specifics.
2. CSA 3 mg/kg CIVI starting day –2 for at least 100 days or Tacrolimus 0.03 mg/kg CIVI starting day –1 for at least 100 days.
3. Mycophenylate mofetil (also known as CellCept) 1000mg orally BID on days 1-40.

V. Tables

<table>
<thead>
<tr>
<th>Drug (Amt/m2 or Amt/kg)</th>
<th>Route</th>
<th>Infusion Rate</th>
<th>Give on Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate 5 mg/m2</td>
<td>IV</td>
<td>slow push</td>
<td>Days (+1), (+3), (+6), (+11)</td>
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</table>

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>MTX Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-1.5 x baseline</td>
<td>Reduce 0-25%</td>
</tr>
<tr>
<td>1.6-1.9 x baseline</td>
<td>Reduce 25-50%</td>
</tr>
<tr>
<td>&gt;1.9 x baseline</td>
<td>Hold</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Amount</th>
<th>Route</th>
<th>Infusion Rate</th>
<th>Give on Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Route: 0.03 mg/kg</td>
<td>CIVI</td>
<td>continuous</td>
<td>Day -1 until Day 180*</td>
</tr>
<tr>
<td>*Oral Route: Total dose 3 times the IV dose, divided and given twice daily</td>
<td>Oral</td>
<td>NA</td>
<td>until Day 180</td>
</tr>
</tbody>
</table>

*Give orally when patient is able to tolerate capsules.

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Tacrolimus Dose</th>
</tr>
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<tbody>
<tr>
<td>1.0-1.5 x baseline</td>
<td>75-100% current dose</td>
</tr>
<tr>
<td>1.6-1.9 x baseline</td>
<td>25-50% current dose</td>
</tr>
<tr>
<td>&gt;1.9 x baseline</td>
<td>hold 12 hours and resume at 50% current dose if renal function stabilizes</td>
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### Table 5: Campath Dosing for GvHD Prophylaxis

<table>
<thead>
<tr>
<th>Drug Amount</th>
<th>Route</th>
<th>Infusion Rate</th>
<th>Give on Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg in 250 ml Normal Saline</td>
<td>IV</td>
<td>over 3 hours</td>
<td>Day -7 through Day -5</td>
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</table>

### Table 6: Cyclosporine A (CSA) Dosing

<table>
<thead>
<tr>
<th>Drug Amount</th>
<th>Route</th>
<th>Infusion Rate</th>
<th>Give on Dates</th>
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</thead>
<tbody>
<tr>
<td>3 mg/kg</td>
<td>IV*</td>
<td>continuous</td>
<td>Day -2 until Day 180*</td>
</tr>
<tr>
<td>*Oral Route: Total dose is 3 times the IV dose, divided and given twice daily</td>
<td>Oral</td>
<td>N/A</td>
<td>Until day 180</td>
</tr>
</tbody>
</table>

**VI. Authors**

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B. 8/2009 Reviewed and Reformatted: Mary Gray
C. 4/2010 Mary Gray, Amber Lawson, Dianna Howard
D. 4/2012 Paige Haydon, Amber Lawson, Dianna Howard
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**VII. References**

2. Graft Versus Host Disease, Romeo A Mandanas, MD, FACP, Director, Western Oklahoma Bone Marrow Transplant Program, Site Research Leader, Cancer Care Associates-Oklahoma City; http://emedicine.medscape.com/article/429037-media

**VIII. See Also:**

A. Appendix A: BMT Physician Orders and Chemotherapy Orders
B. Appendix B: BMT Order Sets and Protocols