DukeMedicine
Division of Cellular Therapy

ADULT AND PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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Prophylaxis and Treatment of Acute GVHD

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APBMT-COMM-013
PROPHYLAXIS AND TREATMENT OF ACUTE GVHD

1 PURPOSE

1.1 To outline the care of the Hematopoietic Stem Cell Transplant (HSCT) patient to prevent and treat acute graft versus host disease (GVHD).

2 INTRODUCTION

2.1 **Supportive Data**: Graft versus host disease is a common complication following allogeneic stem cell transplantation. Acute GVHD usually occurs within the first 100 days after transplant but can occur later in recipients of T-cell depleted or cord blood transplants. Recipients of grafts from mismatched and unrelated donors are at greatest risk for developing GVHD. Chronic GVHD can occur after 100 days and up to a few years post transplant. All allogeneic HSCT patients are placed on prophylactic medications to prevent or ameliorate GVHD. If GVHD occurs, treatment algorithms are defined by type of transplant, type and extent of GVHD and age and performance status of the patient.

3 SCOPE AND RESPONSIBILITIES

3.1 All recipients of allogeneic HSCT are at risk for HSCT.

3.2 All clinical personnel responsible for the oversight of care for patients receiving HSCT are responsible for ensuring that the requirements of this procedure are successfully met.

4 DEFINITIONS/ACRONYMS

4.1	aGVHD	Acute Graft Versus Host Disease
4.2	ATG	Antithymocyte globulin
4.3	FK-506	Tacrolimus
4.4	CYA	Cyclosporine
4.5	GVHD	Graft Versus Host Disease
4.6	HSCT	Hematopoietic Stem Cell Transplant
4.7	MMF	Mycophenolate
4.8	MTX	Methotrexate
4.9	PSE	Prednisone
4.10	RUQ	Right Upper Quadrant

5 MATERIALS

5.1 Computer based weekly GVHD scoring forms

6 EQUIPMENT

6.1 NA

7 SAFETY

7.1 N/A

8 PROCEDURE

8.1 Nursing Assessment:

8.1.1 Assess q shift for symptoms of acute GVHD of the skin, liver, and gut.

8.1.1.1 Typically the first sign of skin GVHD is a mild rash, usually on upper chest, back, and arms.

8.1.1.2 Diarrhea is the usual first sign of gut GVHD; assess for stool volume, color, and consistency.

8.1.1.3 Anorexia can be a sign of upper gut GVHD.

8.1.1.4 Elevated bilirubin is usually the first sign of liver GVHD, although it is not diagnostic.

8.2 Prevention and treatment of acute GVHD: Note that new studies for prevention and treatment of GVHD are ongoing. Review new protocols before administering new therapies.

8.3 Prophylactic measures:

8.3.1 Immunosuppressants are used to reduce the patient's natural immunity and to prevent the transplanted cells from attacking the host cells.

8.3.1.1 Cyclosporine (CYA): Inhibits and suppresses T-lymphocytes. Calcineurin inhibitor resulting in inhibition of IL-2 production and decreased proliferation of antigen-specific T-lymphocytes.

8.3.1.2 Tacrolimus (FK-506): Binds to a T-cell protein and prevents synthesis of IL-2 and other lymphokines essential to T-cell function. Calcineurin inhibitor resulting in inhibition of IL-2 production and decreased proliferation of antigen-specific T-lymphocytes.

8.3.1.3 Methotrexate (MTX): An antimetabolite that interferes with DNA synthesis; used in low doses shortly after transplant to prevent GVHD.

8.3.1.4 Prednisone (PSE): Inhibits production of T-cell lymphokines that are needed to amplify macrophage and lymphocyte response.

8.3.1.5 Mycophenolate Mofetil (Cellcept; MMF): Inhibits purine synthesis inhuman lymphocytes which, in turn inhibits lymphocyte proliferation. MMF works through active

metabolite mycophenolic acid on proliferating lymphocytes by noncompetitively inhibiting both isoforms of inosine monophosphate dehydrogenase, the rate limiting enzyme in de novo purine synthesis.

8.3.1.6 Sirolimus (Rapamycin): Inhibits activation of mammalian target of rapamcin (MTOR), thus preventing T-Cell activation and proliferation.

8.3.1.7 Antithymocyte globulin (ATG): Eliminates antigen T-lymphocytes and alters T-cell function.

8.4 Treatment of acute GVHD:

8.4.1 Immunosuppressants are used to reduce the patient's natural immunity and to prevent the transplanted cells from attacking the host cells.

8.4.1.1 High dose steroids typically consisting of either prednisone or methylprednisolone dosed at 2mg/kg/day (max 1000mg/day).

8.4.1.2 Switch from Cyclosporine to Tacrolimus or from Tacrolimus to Cyclosporine.

8.4.1.3 Apply topical Tacrolimus ointment and/or steroid skin creams to affected skin areas.

8.4.1.4 Various monoclonal antibodies designed to kill T-lymphocytes: Alemtuzumab (anti-CD52), rituximab (anti-CD20), infliximab (anti-TNF) and Tocilizumab (anti Interleukin-6))

8.4.1.5 Cyclosporine (CYA): inhibits and suppresses T-lymphocytes

8.4.1.6 Calcineurin inhibitor resulting in inhibition of IL-2 production and decreased proliferation of antigen-specific T-lymphocytes.

8.4.1.7 Tacrolimus (FK-506): Binds to a T-cell protein and prevents synthesis of IL-2 and other lymphokines essential to T-cell function. Calcineurin inhibitor resulting in inhibition of IL-2 production and decreased proliferation of antigen-specific T-lymphocytes.

8.4.1.8 Methotrexate (MTX): An antimetabolite that interferes with DNA synthesis; used in low doses shortly after transplant to prevent GVHD.

8.4.1.9 Prednisone (PSE): inhibits production of T-cell lymphokines that are needed to amplify macrophage and lymphocyte response.

8.4.1.10 Mycophenolate Mofetil (Cellcept; MMF): Inhibits purine synthesis of human lymphocytes as well as the proliferation of lymphocytes. MMF works through its active metabolite

mycophenolic acid on proliferating lymphocytes by noncompetitively inhibiting both isoforms of inosine monophosphate dehydrogenase, the rate limiting enzyme in de novo purine synthesis.

8.4.1.11 Sirolimus (Rapamycin): Inhibits activation of mammalian target of rapamcin (MTOR), thus preventing T-Cell activation and proliferation.

8.4.1.12 Antithymocyte globulin (ATG): Eliminates antigen T-lymphocytes and alters T-cell function; available in both equine and rabbit formulation.

8.4.1.13 Denileukin diftitox (Ontak): Anti CD25

8.4.1.14 Rituximab: Anti CD20 antibody linked to ricin.

8.4.1.15 Infliximab: Anti TNF antibody.

8.4.1.16 Tocilizumab: Antagonist of Interleukin-6 (IL-6) receptor

8.4.1.17 Etanercept: Anti TNF antibody.

8.4.1.18 Pentostatin: Inhibits adenosine deaminase causing lymphocytotoxicity.

8.4.1.19 Ruxolitinib: JAK1/2 inhibitor

8.5 Skin GVHD:

8.5.1 Assess for signs of skin GVHD:

8.5.1.1 Maculopapular rash on trunk, palms, soles, or ears.

8.5.1.2 Generalized erythroderma with or without desquamation.

8.5.1.3 Bullous (blister) formation and/or skin breakdown.

8.5.2 Staging of skin GVHD

8.5.2.1 Stage 1: Maculopapular rash on <25% of skin.

8.5.2.2 Stage 2: Rash on 25-50% of skin.

8.5.2.3 Stage 3: Rash on >50% of skin.

8.5.2.4 Stage 4: Generalized erythroderma with bullous formation.

8.5.3 Interventions in skin GVHD:

8.5.3.1 Use Chlorhexidine soap, no bar soap.

8.5.3.2 Apply Aquaphor cream to dry skin as ordered.

8.5.3.3 Keep skin clean and nails short.

8.5.3.4 Administer topical steroids, tacrolimus-based cream, and antihistamine cream as ordered.

8.5.3.5 Initiate Pressure Ulcer Prevention and/or Treatment Plan of Care.

8.5.3.6 Consult skin care nurse and consider specialty bed.

8.6 Gut GVHD:

8.6.1 Assess for signs of gut GVHD:

8.6.1.1 Watery diarrhea, sometimes green (bilious), or bloody.

8.6.2 Abdominal cramping/pain.

8.6.3 Anorexia, nausea, vomiting.

8.6.4 GI bleeding.

8.6.5 Quantify all diarrhea to assist in staging process.

8.6.6 Staging of gut GVHD:

8.6.6.1 Stage 1: Diarrhea > 500 mL/day (adults) or > 280 mL/m^2 (children) or persistent nausea.

8.6.6.2 Stage 2: Diarrhea > 1000 mL/day (adults) or > 555 mL/m^2/day (children).

8.6.6.3 Stage 3: Diarrhea > 1500 mL/day (adults) or > 833 mL/m^2/day (children).

8.6.6.4 Stage 4: Diarrhea and severe abdominal pain with or without ileus.

8.6.7 Interventions in gut GVHD:

8.6.7.1 Report stool volume of > 500 ml/24 hours (adults) or volumes referenced in section "g" for children.

8.6.7.2 Obtain daily weights.

8.6.7.3 Monitor I and O's strictly while in hospital.

8.6.7.4 Monitor ABC's q day as ordered.

8.6.7.5 Monitor electrolytes closely replace electrolytes per orders.

8.6.7.6 Monitor liver function tests as requested by MD, minimally weekly.

8.6.7.7 Administer anti-emetics per MD order around the clock and prn.

8.6.7.8 Administer anti-diarrheals per MD order. Do not give if signs of toxic colon present.

8.6.7.9 Anticipate endoscopy and gut biopsy during endoscopy.

8.6.7.10 Administer analgesics for abdominal pain per MD order.

8.6.7.11 Obtain nutritional consult and anticipate TPN therapy.

8.6.7.12 Limit oral intake if MD order.

8.6.7.13 Consider octreotide.

8.7 Liver GVHD:

8.7.1 Assess for signs of liver GVHD:

8.7.1.1 Jaundice

8.7.1.2 Elevated bilirubin, GGT or alkaline phosphatase.

8.7.1.3 Hepatomegaly

8.7.1.4 Ascites

8.7.1.5 RUQ pain.

8.7.1.6 Weight gain.

8.7.1.7 If appropriate, obtain liver US to r/o VOD.

8.7.2 Staging of liver GVHD:

8.7.2.1 Stage 1: Bilirubin 2-3 mg/dl.

8.7.2.2 Stage 2: Bilirubin 3.1-6 mg/dl.

8.7.2.3 Stage 3: Bilirubin 6.1-15 mg/dl.

8.7.2.4 Stage 4: Bilirubin > 15 mg/dl.

8.7.3 Interventions in liver GVHD:

8.7.3.1 Monitor liver and renal function tests as ordered.

8.7.3.2 Monitor I and O and daily weights strictly while in hospital.

8.7.3.3 Anticipate possible liver biopsy.

8.7.3.4 Anticipate an increase in corticosteroids or other immunosuppressive therapy.

8.7.3.5 Avoid hepatotoxic drugs, i.e. acetaminophen, voriconazole plus fluconazole

8.7.3.6 NB: Fluconazole and voriconazole decrease clearance of Cyclosporine and Tacrolimus. Patients taking concomitant azoles and immunosuppressants should have more frequent monitoring of CSA and FK levels. These patients may require dose reduction of their immunosupressive therapy.

8.8 Reportable Conditions:

8.8.1 Signs of skin GVHD: Maculopapular rash on trunk, palms, soles, or ears; generalized erythroderma with desquamation; bullous (blister) formation and/or skin breakdown.

8.8.2 Signs of gut GVHD: Diarrhea, abdominal cramping/pain, anorexia, nausea, vomiting, GI bleeding.

8.8.3 Signs of liver GVHD: Jaundice, elevated bilirubin or alkaline phosphatase, hepatomegaly, ascites, RUQ pain, sudden weight gain.

9 RELATED DOCUMENTS/FORMS

9.1 N/A

10 REFERENCES

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11 REVISION HISTORY

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