DukeMedicine
Division of Cellular Therapy

ADULT AND PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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Prophylaxis and Treatment of Chronic GVHD

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APBMT-COMM-038
PROPHYLAXIS AND TREATMENT OF CHRONIC GVHD

1 PURPOSE

1.1 To outline the care of the Hematopoietic Stem Cell Transplant (HSCT) patient to prevent and treat chronic 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.

2.2 Patients at higher risk of chronic GVHD include those receiving unrelated donor or mismatched transplants, those who experience acute GVHD, those who have older, multiparous adult female donors, those who are of older age, those who cannot tolerate acute GVHD prophylaxis and those who are transplanted with PBPC grafts.

2.3 Level: Interdependent (* requires an order to be placed in EPIC from physician or physician designee).

3 SCOPE AND RESPONSIBILITIES

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

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	AIHA	- Autoimmune hemolytic anemia
4.2	ANA	- Avascular necrosis
4.3	ATG	- Antithymocyte globulin
4.4	FK-506	- Tacrolimus
4.5	CTN	- Clinical Trials Network
4.6	CYA	- Cyclosporine
4.7	GGT	- Gamma-glutamyltransferase
4.8	GI	- Gastrointestinal
4.9	GVHD	- Graft Versus Host Disease

4.10 HSCT - Hematopoietic Stem Cell Transplant

4.11 IVIG - Intravenous Immunoglobulin

4.12 ITP - Immune thrombocytopenia

4.13 MMF - Mycophenolate

4.14 MTX - Methotrexate

4.15 PSE - Prednisone

4.16 RUQ - Right Upper Quadrant

5 MATERIALS

5.1 Computer based chronic GVHD scoring forms, CTN forms attached.

6 EQUIPMENT

6.1 NA

7 SAFETY

7.1 NA

8 PROCEDURE

8.1 Nursing and Physician Assessment:

8.1.1 Assess at clinic visits for symptoms of chronic GVHD of the skin, liver, gut, lungs, endocrine function, immune system, bones and joints, eyes, mouth, nails, and genitalia.

8.1.1.1 Chronic GVHD can cause varying types of skin rashes, frequently mimicking eczema, dry skin or chronic atopic dermatitis. Hyperpigmentation of skin and hair loss are common. Abnormalities of nails and nail beds can occur. Chronic lip dryness, cracking and mouth ulcers can be seen. In severe cases, scleroderma can occur and lead to fatalities.

8.1.1.2 Chronic GVHD can affect the upper or lower GI tract, possible symptoms of upper gut disease include:

8.1.1.2.1 Anorexia

8.1.1.2.2 Weight loss

8.1.1.2.3 Nausea

8.1.1.2.4 Vomiting

8.1.1.3 Diarrhea, often with abdominal pain and cramping, is the usual first sign of lower gut GVHD; assess for stool volume, color, and consistency. Pancreatic insufficiency may result in decreased production and secretion of pancreatic enzymes.

8.1.1.4 Chronic GVHD of the liver will usually present with jaundice (hyperbilirubinemia), accompanied by elevation of the alkaline phosphatase (hepatic component) and/or GGT. In some instances, hepatic transaminases are also elevated. Liver biopsy is necessary to obtain a definitive diagnosis.

8.1.1.5 Chronic GVHD can impair immune reconstitution, particularly thymic function, leading to increased morbidity and mortality from opportunistic infections.

8.1.1.6 Chronic GVHD can also cause immune mediated cytopenias (AHA, ITP, AN); joint disease; uveitis; dry eyes, myositis, myasthenia gravis, etc.

8.1.1.7 Bronchiolitis Obliterans with pulmonary insufficiency and/or failure is a manifestation of chronic GCHD. Chronic wheezing/asthmatic bronchitis may be seen. Chronic and recurrent sinusitis is also common.

8.1.1.8 Chronic GVHD can impair endocrine function leading to low estrogen, testosterone and symptoms resulting from deficiencies of these hormones. In children, chronic GVHD and its treatment can impair skeletal growth.

8.1.1.9 Rarely chronic GVHD has been reported to involve bladder wall, thymus, pancreas and brain.

8.2 Prevention and treatment of chronic 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. Prophylaxis against acute GVHD helps reduce the risk of chronic GVHD.

8.3.1.1 Cyclosporine (CYA): inhibits and suppresses T lymphocytes. Cyclosporine inhibition of calcineurin results in the 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): is 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 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.

8.3.1.6 Sirolimus (Rapamycin): blocks CD28 co-stimulatory signaling.

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

8.4 Treatment of chronic GVHD:

8.4.1 Immunosuppressants prevent the transplanted cells from attacking the host cells.

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

8.4.1.2 Switch from cyclosporine to tacrolimus or tacrolimus to cyclosporine

8.4.1.3 Apply topical tacrolimus and steroid skin creams to affected skin areas.

8.4.1.4 Various monoclonal antibodies designed to affect T lymphocytes. (e.g. basiliximab (Simulect), alemtuzumab (Campath - anti CD52), rituximab (anti CD20) and Tocilizumab (anti Interleukin-6).

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

8.4.1.6 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.

8.4.1.7 Azathioprine (Imuran): inhibits nucleoside synthesis, inhibiting T and B-cell proliferation.

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

8.4.1.9 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.

8.4.1.10 Sirolimus (Rapamycin): blocks CD28 co-stimulatory signaling.

8.4.1.11 Antithymocyte globulin (ATG): eliminates antigen T-lymphocytes and alters T-cell function; available in both equine and rabbit formulations.

8.4.1.12 Basiliximab: Anti CD25, kills activated T-cells expressing CD25 antigen

8.4.1.13 Rituximab: Anti CD20 antibody linked to ricin.

8.4.1.14 Infliximab: Anti TNF antibody.

8.4.1.15 Tocilizumab: Antagonist of interleukin-6 (IL-6) receptor

8.4.1.16 Etanercept: Anti TNF antibody.

8.4.1.17 Pentostatin: inhibits adenosine deaminase causing lymphocytotoxicity.

8.4.1.18 Photopheresis

8.4.1.19 Ruxolitinib: JAK1/2 inhibitor

8.4.1.20 Imatinib: tyrosine kinase inhibitor

8.4.1.21 Ibrutinib: tyrosine kinase inhibitor

8.4.1.22 Interleukin-2: IL-2

8.4.1.23 Abatacept: T-cell blocker

8.4.1.24 Hydroxychloroquine: aminoquinolone

8.4.1.25 Belumosudil: ROCK-2 inhibitor

8.5 Supportive care of the patient with chronic GVHD: See attached NIH consensus articles for additional details.

8.5.1 Prophylaxis against infection

8.5.1.1 Fungal

8.5.1.2 Viral

8.5.1.3 Bacterial – encapsulated organisms

8.5.1.4 IVIG

8.5.1.5 Immunizations, if immune function sufficient for response

8.5.2 Skin/Eye/Mouth care

8.5.2.1 Steroids

8.5.2.2 Protopic/Eladil

8.5.2.3 Moisturizing agents for skin and eyes

8.5.2.4 Mouthwashes, artificial saliva, oral non-absorbable steroids

8.5.2.5 Sunscreen

8.5.2.6 Avoid direct sun exposure

8.5.2.7 Avoid perfumes, bubble bath, drying soaps, detergents

8.5.3 Lung

8.5.3.1 Inhaled steroids

8.5.3.2 Bronchodilators

8.5.3.3 Oxygen support, Bipap

8.5.4 GI

8.5.4.1 Avoid lactose

8.5.4.2 High calorie diet, frequent snacks

8.5.4.3 Pancreatic enzyme supplements

8.5.4.4 If diarrhea occurs: consider utilization of anti-spasmotics and/or anti-diarrheals

8.6 Reportable Conditions:

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

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

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

8.7 The adult GVHD flowsheet will be reviewed annually by physician leadership.

9 RELATED DOCUMENTS/FORMS

9.1 N/A

10 REFERENCES

10.1 Buchsel, PC and PM Kapustay, Eds. Stem Cell Transplantation: A Clinical Textbook. Oncology Nursing Press, Pittsburgh PA. 2000.

10.2 Goker, H., et al. Acute graft vs host disease: Pathobiology and management. Experimental Hematology. 29 (2001) 259-277.

10.3 Graft-Versus-Host-Disease. Blood & Marrow Transplant Newsletter. December 2000. Available www.bmtinfonet.org/newsletters/issue52/graftversus.html

10.4 Biology of Blood and Marrow Transplantation 2005-6: National Institutes of Health Consensus Develop Project of Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: I-VI.

10.5 Hymes, S, Turner, ML, Champlin RE, Couriel DR. Cutaneous Manifestations of Chronic Graft -Versus-Host Disease. Biology of Blood and Marrow Transplantation 12:1101-1113, 2006.

10.6 Blood. 2015 Jan 22;125(4):606 15.

10.7 Pharmacotherapy. 2020 Aug;40(8):756 772.

10.8 Biol Blood Marrow Transplant. 2015 Jun;21(6):984 99.

10.9 Zeiser R, et al. N Engl J Med. 2021 Jul 15;385(3):228 238

10.10 NCCN Clinical Practice Guidelines. Hematopoietic cell transplantation (HCT): Version 5.2021. September 30, 2021.

10.11 Jagasia M, et al. Clin Oncol. 2021;39(17):1888-1898

11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
05	MC Authors: McCollum/Frith SMEs: Elizabeth Rogers Jill Lawrence Lauren Stafford Paul Martin Tim Driscoll	- Section 8.1: added eyes, mouth, scalps, nails. genitalia - Section 8.4: additional agents added - imatinib (tyrosine kinase inhibitor), ibrutinib (Bruton tyrosine kinase inhibitor), interleukin-2 (IL-2), Abatacept (T-cell blocker), hydroxychloroquine (aminoquinolone), ruxolitinib (JAK 1/2 inhibitor) and belumosudil (ROCK-2 inhibitor) - Section 8.4.1: minor wording update for clarity - Added 8.7 GVHD adult flowsheet will be reviewed annually - Section 10: additional references added

Signature Manifest

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