Blood and Marrow TRANSPLANTATION

REVIEWS

A Publication of the American Society for Blood and Marrow Transplantation

Issues in Hematology, Oncology, and Immunology VOLUME 17 NO 4 2007

IN THIS ISSUE

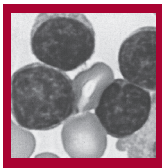
Graft-versus-Host Disease: The Pesky Fly in the Ointment

John R. Wingard, MD, Editor

The alloreactive potency of the hematopoietic stem cell graft provides powerful anticancer activity. Unfortunately, the potential for harm (by graft-versus-host disease [GVHD]) is often as strong as the potential for good. The measures used to control GVHD, such as steroids and antithymocyte globulin, often seem like elephant guns causing similar harmful effects (toxicity and vulnerability for infection) as the GVHD itself, and they rob much of the anticancer effects of the donor graft. GVHD is indeed the thorniest problem of allogeneic hematopoietic cell transplantation (HCT). What can be done?

This issue contains a written adaptation of a symposium that addresses the topic of new strategies for GVHD. This symposium was presented at the 2007 BMT Tandem Meetings in Keystone, Colorado. Drs. Jacobsohn, Chen, and Chan describe a variety of opportunities to improve control of GVHD. As they note, the quest for GVHD control begins with donor selection. Manipulation of the conditioning regimen also holds promise. Stem cell graft engineering has taken on new life due to better understanding of how various cell populations function and interact and better techniques to characterize, isolate, and expand them by both ex vivo and in vivo tools. Finally, posttransplantation immunosuppressive regimens have historically been useful in reducing severe acute GVHD but have left unaffected chronic GVHD; now, new immunosuppressive agents are in clinical trials to test if they are more effective or provide safety advantages. Ultimately, exquisite engineering of the donor graft or staged infusions of specific cell populations may be necessary to optimize the beneficial immunotherapeutic effects of HCT. Alternatively, incremental progress in the multiple facets of the various elements of transplantation including donor selection, conditioning regimen, posttransplantation immunosuppressive regimens, and cellular engineering may get us what we need. GVHD has been the pesky fly in the ointment of HCT.

For an ointment to be truly a healing unguent, impurities must not deter its use; for HCT to be more widely applied for human disease, serious complications such as GVHD must be better controlled.



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Publishing and Production Services
CJP Medical Communications, a division of Carden Jennings Publishing Co., Ltd.

Blood and Marrow Transplantation Reviews is published quarterly by CJP Medical Communications.
375 Greenbrier Dr., Suite 100, Charlottesville, VA 22901
phone (434) 817-2000; fax (434) 817-2020

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The opinions and recommendations expressed herein are those of the individual authors and in no way reflect those of the society, sponsor, or Carden Jennings Publishing.

This publication is supported by an educational grant from Hospira, Inc.

PRELIMINARY APPLICATION

Be a part of a national organization established to promote education, research, and medical development in the field of blood and marrow transplantation.

Full Membership is open to individuals holding an MD or PhD degree with demonstrated expertise in blood and marrow transplantation as evidenced by either the publication of two papers on hematopoietic stem cell transplantation–related research as recorded by curriculum vitae, or documentation of two years of experience in clinical transplantation as recorded by curriculum vitae or letter from the director of a transplant center attesting to the experience of the candidate.

Associate Membership is open to individuals with an MD or PhD degree who otherwise do not meet the criteria for full membership.

Affiliate Membership is available to allied non-MD or non-PhD professionals who have an interest in blood and marrow transplantation. This category is especially appropriate for nursing and administrative staff of bone marrow transplant centers, collection centers, and processing laboratories, and for professional staff of corporations that provide products and services to the field of blood and marrow transplantation.

In-Training Membership is open to fellows-in-training in bone marrow transplantation programs. A letter from the transplant center director attesting to the applicant's training status is required.

Included in the membership fee is a one-year subscription to ***Biology of Blood and Marrow Transplantation.***

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2008 BMT TANDEM MEETINGS WILL BE FEB. 13-17 IN SAN DIEGO

The combined 2008 annual meetings of ASBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR) will be February 13-17 at the Manchester Grand Hyatt Hotel in San Diego, California.

Recent advances in the broad field of cellular therapy and blood and marrow transplantation will be addressed in plenary sessions, concurrent sessions, workshops, poster sessions and symposia. In addition to the program highlights listed below, 78 original abstracts will be selected for oral presentation.

Wednesday, February 13

- Graft versus Leukemia
  Stanley Riddell, Warren Shlomchik, Michael Jensen
- Summary of BMT State of the Science Symposium
  James Ferrara, Daniel Weisdorf, Mary Horowitz, Joseph Antin
- AL Amyloidosis: the New, the Old and the Role of High-Dose Chemotherapy with Stem Cell Support
  Angela Dispenzieri, Raymond Comenzo, Giampaolo Merlin
- Cancer Stem Cells
  Scott Armstrong, Richard Jones, Catriona Jamieson
- Mortimer M. Bortin Lecture
  John Goldman

Thursday, February 14

- Stem Cell Interactions and Kinetics
  David Scadden, Willem Fibbe, Janis Abkowitz
- Memory T-Cells
  Warren Shlomchik, Benny Chen, Stanley Riddell
- Endothelial Biology and Transplant-Related Complications
  Kenneth Cooke, Anne Janin, Vincent Ho
- CIBMTR/EBMT Key Studies
  Sergio Giralt

Friday, February 15

- Tolerance Induction for Hematopoietic and Solid Organ Graft Acceptance
  Christian Larsen, Yair Reisner, Bruce Blazar
- Clinical Strategies to Enhance Post-Transplant Immune Reconstitution
  Marcel van den Brink, Irwin Bernstein, Richard Boyd
- Controversies in Lymphoma
  Izidore Lossos, Ginna Laport, Peter Dreger
- Selecting Donors and Cord Blood Units: Evidence-Based Decisions (NMDP Session)
  Dennis Confer, Stephanie Lee, Naynesh Kamani
- Best Abstracts Session
- E. Donnall Thomas Lecture
  John A. Hansen

Saturday, February 16

- HumanPolymorphism and the Outcome of Therapy
  Stella M. Davies, Jeffrey Miller, Anne Dickinson
- Mouse Models of BMT
  Geoff Hill, Robert Negrin, Pavan Reddy
- T-Cell Therapy
  Helen Heslop, Frederik Falkenburg, John Barrett
- Chronic GVHD: How Can We Release Prometheus?
  Paul Martin, Takanori Teshima, Thomas Wynn, Robert Soiffer
- Stem Cells and Regenerative Medicine
  Jan Nolta, Evan Snyder, Mariusz Ratajczak

Sunday, February 17

- Transplants for Acute Leukemia
  Frederick Appelbaum, Stella Davies, Jacob Rowe
- The Aging Stem Cell and its Niche: Implications for Stem Cell Function, Transplantation and Transformation
  Gary Van Zant, Lenhard Rudolph, James DeGregori
- Graft Failure after Hematopoietic Stem Cell Transplantation
  Olle Ringdén, Rainer Storb, Jonas Mattsson

The scientific program chair for ASBMT is Marcel van den Brink, MD, PhD, of Memorial Sloan-Kettering Cancer Center, and chair for the CIBMTR is Stella M. Davies, MD, PhD, of Cincinnati Children's Hospital.

RELATED CONFERENCES

In addition to the five days of scientific sessions for BMT clinicians and investigators, there will be six related conferences and courses:

- Clinical Research Professionals/Data Management *(Feb. 12-14)*
- BMT Center Administrators *(Feb. 13-14)*
- Pediatric BMT *(Feb. 14)*
- Transplant Nursing *(Feb. 15-17)*
- BMT Pharmacists *(Feb. 15-17)*
- BMT Center Medical Directors *(Feb. 16)*

EARLY REGISTRATION

The early registration deadline is October 8. Online meeting registration can be accessed at both the ASBMT Web site, *www.asbmt.org*, and the CIBMTR Web site, *www.cibmtr.org*. Information is updated continuously.

ABSTRACT SUBMISSION

Abstracts can be submitted for the BMT Tandem Meetings on either of the two Web sites. The deadline is October 8.

HOUSING

Lodging accommodations also can be accessed on either Web site. The housing deadline is January 11, 2008, after which accommodations are on a space-available basis.

BLOOD STEM CELL TRANSPLANTS EXCEED 16,000 YEARLY IN U.S.

Currently more than 16,000 hematopoietic stem cell transplants are performed annually in the United States, according to estimates from the Center for International Blood and Marrow Transplant Research (CIBMTR).

Based on data submitted by participating transplant centers, the CIBMTR estimates that the numbers of transplants in 2005 were:

Autologous – 10,000
Related allogeneic – 3,500
Unrelated allogeneic – 2,250
Cord blood – 550

Detailed information about transplant indications, recipient age, graft sources, transplant regimens and outcomes can be found on the CIBMTR Web site at www.cibmtr.org.

ASBMT

Symposium Report

Blood and Marrow TRANSPLANTATION REVIEWS

Current Advances in the Treatment of Acute and Chronic Graft-versus-Host Disease

Adapted from a continuing medical education symposium presented at the BMT Tandem Meetings on February 7, 2007, in Keystone, Colorado.
This program is supported by an unrestricted educational grant from Hospira, Inc.

MEDICAL COLLEGE OF WISCONSIN CME program

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Needs Assessment

Graft-versus-host disease (GVHD) is the leading cause of procedural-related morbidity and mortality in patients receiving allogeneic transplants. Immunosuppressive agents are often administered following transplantation to decrease the incidence and severity of GVHD. This commonly includes corticosteroids and cyclosporin A or the macrolide FK506, which are designed to suppress donor T-cell function, coupled with methotrexate to inhibit T-cell proliferation. Current research efforts are focusing on the development of more effective and less-toxic therapeutic options to reduce procedure-related morbidity and mortality. Other strategies involve manipulation of the allograft to eliminate or anergize alloreactive cells or alternatively, to provide immunoregulatory cells that inhibit development of GVHD.

An increased understanding of the immune events that follow hematopoietic stem cell transplantation has resulted in the investigation of several agents capable of disrupting the GVHD cycle, including the use of purine analogs both in the treatment and prophylaxis of GVHD. Investigations are ongoing to determine if such therapy will improve engraftment and reduce morbidity and mortality.

Target Audience

This activity is intended for transplantation physicians and allied health professionals.

Learning Objectives

- Assess the major factors that contribute to the morbidity and mortality associated with GVHD in patients undergoing stem cell transplantation.
- Based on results from recent clinical trials, discuss the efficacy of the novel strategies that are currently being investigated for the prevention and management of GVHD.

Accreditation Statement

The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation of Credit

The Medical College of Wisconsin designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclaimer

This material has been prepared based on a review of multiple sources of information, but it is not exhaustive of the subject matter. Participants are advised to critically appraise the information presented, and are encouraged to consult the above-mentioned resources as well as available literature on any product or device mentioned in this program.

Disclosure of Unlabeled Uses

This educational activity may contain discussion of published and/or investigational uses of agents that are not approved by the US Food and Drug Administration. For additional information about approved uses, including approved indications, contraindications, and warnings, please refer to the prescribing information for each product, or consult the Physician's Desk Reference. This presentation contains discussion of the off-label use of ATG, daclizumab, denileukin diftitox, etanercept, infliximab, mycophenolate mofetil, pentostatin, rapamycin, rituximab, sirolimus, and tacrolimus.

Faculty Disclosure

Consistent with the current Accreditation Council for Continuing Medical Education policy, the provider must be able to show that everyone who is in a position to control the content of an individual educational activity has disclosed all relevant financial relationships. The presenting faculty members have all made the proper disclosures, and the following relationships are relevant:

The faculty have declared the following relevant financial relationships:

Allen R. Chen, MD, PhD, MHS: consultant for SuperGen; stockholder in Amgen.

Geoffrey W. Chan, MD: speaker for Therakos, Ligand, SuperGen, and GlaxoSmithKline.

David A. Jacobsohn, MD: consultant and speaker for SuperGen.

INTRODUCTION

Approximately 8000 allogeneic bone marrow transplantations are performed annually in the United States; graft-versus-host disease (GVHD), which was first defined in the 1950s, is a major hindrance to the success of these transplantations [1]. GVHD occurs in acute and chronic forms. Acute GVHD usually manifests within 20 to 40 days following transplantation. Chronic GVHD has a later onset and may develop as an extension of acute GVHD, following resolution of acute GVHD, or de novo [2]. Of patients receiving allogeneic stem cell transplants, severe acute GVHD occurs in 9% to 35%, and chronic GVHD occurs in 40% to 50% [1,3,4]. The incidence of GVHD is increasing due to enlargement of the donor pool, including more transplants from unrelated and mismatched donors as well as more transplantations in older recipients [5]. Although GVHD is a source of significant morbidity and mortality, mild acute and chronic GVHD are associated with a beneficial antitumor effect [6,7].

ACUTE GVHD

Incidence/Symptoms/Grading

Acute GVHD is a frequent complication of stem cell transplantation and donor lymphocyte infusions, usually occurring around the time of engraftment in myeloablative transplantations. The incidence of grade 2 to 4 acute GVHD is approximately 35% among patients receiving stem cells from a human leukocyte antigen (HLA)-identical sibling donor [3,4]. GVHD occurs in 70% to 80% of patients following donor lymphocyte infusion and its incidence is increased among older patients, patients receiving matched unrelated donor transplants, and patients positive for cytomegalovirus (CMV) [8-10]. The mortality for acute GVHD can be as high as 50% [11].

Acute GVHD affects the skin, gastrointestinal tract, and liver. The stage of GVHD is determined by a system that quantifies the extent of skin involvement (rash), diarrhea, and serum bilirubin level [5]. After each organ system has been staged, the grade of GVHD can be determined by comparing the stage of disease in each organ to the Keystone criteria for grading (Table 1 [5]). The severity of acute GVHD correlates directly with survival [6]. However, patients with acute grade 1 GVHD have better survival than patients with no GVHD, presumably due to the graft-versus-tumor effect (Figure 1 [6]).

Pathogenesis

GVHD occurs when graft-derived donor T-cells recognize major histocompatibility (MHC) proteins and associated peptides on host-derived antigen-presenting cells. The pathophysiology of acute GVHD is complex and occurs in 3 phases [12]:

(1) Injury to the host tissues environment, which causes release of inflammatory mediators and increased expression of HLA molecules and cell adhesion proteins;

(2) Activation of donor T-cells followed by their proliferation and differentiation;

(3) Cellular and inflammatory attack on host-target tissues.

The earliest phase of acute GVHD occurs prior to the infusion of donor cells and is due to the effects of the conditioning regimen. Clinical observations show that an enhanced risk of acute GVHD is associated with intensive conditioning regimens [13,14]. These cause extensive damage to cell surfaces, causing release of inflammatory cytokines. The release of these cytokines induces increased expression of cell surface receptors [13]. The relationship between conditioning intensity, inflammation, and GVHD severity has been confirmed by several murine models of GVHD [13,15].

The second phase of acute GVHD involves activation of donor T-cells followed by their proliferation and stimulation [13]. Adherence of donor-derived T-cells to MHC/peptide complexes on a recipient antigen-presenting cell induces activation of T-cell genes, such as nuclear factor-kappa B, resulting in T-cell proliferation and differentiation [16]. During this phase, some alloreactive T-cells may be deleted; however, activated T-cells escaping deletion will undergo differentiation that is characterized by secretion of cytokines and chemokines, particularly IL-2, which may play an important role in the pathogenesis of acute GVHD.

The final phase of acute GVHD involves a cellular and inflammatory attack on the host. Initially, it was thought that the cytolytic action of cytotoxic T lymphocytes directly mediated most of the tissue damage in GVHD. However, preclinical studies indicate that the situation is more complex with large granular lymphocytes or natural killer cells also playing a role in the pathogenesis of acute GVHD [13,17,18]. Mononuclear phagocytes, which were primed in the second phase of the GVHD, secrete IL-1 and tumor necsosis factor alpha (TNF-α) in response to a second activator, which may be endotoxin [13]. These inflammatory cytokines can directly cause damage of host-derived tissue. In addition, T-cells can cause cytolysis directly through cell-to-cell contact, or indirectly through secretion of cytokines such as TNF-α.

Table 1. Recommended Staging and Grading of Acute Graft-versus-Host Disease [5]

	Extent of Organ Involvement		
Stage	Skin	Liver	Gut
I	Rash on <25% of skin*	Bilirubin 2-3 mg/dL†	Diarrhea >500 mL/day‡ or persistent nausea§
II	Rash on 25% to 50% of skin	Bilirubin 3-6 mg/dL	Diarrhea >1000 mL/day
III	Rash on >50% of skin	Bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day
IV	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade‖			
1	Stage I-II	None	None
2	Stage III or	Stage I or	Stage I
3	–	Stage II-III or	Stage II-IV
4¶	Stage IV or	Stage IV	–

*Use "Rule of Nines" or burn chart to determine extent of rash.

†Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

‡Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging criteria for pediatric patients was not discussed at the Consensus Conference. Downgrade one stage if an additional cause of diarrhea has been documented.

§Persistent nausea with histologic evidence of graft-versus-host disease in the stomach or duodenum.

‖Criteria for grading given as minimum degree of organ involvement required to confer that grade.

¶Grade 4 may also include lesser organ involvement but with extreme decrease in performance status.

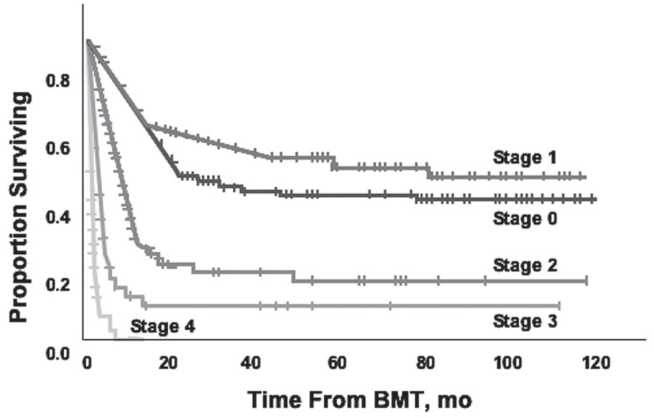

Figure 1. Survival by acute graft-versus-host disease grade. BMT indicates bone marrow transplantation. This figure was published in: *Transplantation,* Volume 67. Nevo S, Enger C, Swan V, et al. Acute bleeding after allogeneic bone marrow transplantation: association with graft versus host disease and effect on survival. 681-689. Copyright Elsevier 1999.

Prevention of Acute GVHD

Current Standard of Care

HLA matching of the donor and recipient represents an effective means of preventing GVHD [19]. However, HLA-matched donors are not always available. Factors such as age and matching the sex of the donor and recipient also predict the risk of GVHD. The use of a young HLA-matched, sex-matched donor in a sterile environment can minimize GVHD. Unfortunately, perfect donors are not always available, so alternative means of preventing GVHD must be employed.

Posttransplantation immunosuppressive therapy represents the most common form of drug-based prophylaxis in HLA-identical and unrelated donors [19]. Generally, the regimen consists of cyclosporine A (CsA; 1 mg/kg) along with a short course of methotrexate (MTX) [20]. Although higher doses of CsA are more effective at controlling GVHD, this benefit is offset by an increased frequency of leukemia relapse with high-dose CsA [21].

An alternative to CsA is the calcineurin inhibitor tacrolimus (FK506). Recipients (n = 329) of HLA-identical sibling bone marrow transplants were randomized in a phase III trial to receive a short course of MTX with tacrolimus or CsA [22]. The incidence of grade 2-4 acute GVHD was significantly lower in patients receiving tacrolimus (32% versus 44%; $P = .01$). Although the incidence of chronic GVHD was similar in both groups (56% versus 49%; $P = .8$), the development of severe chronic GVHD was more likely with CsA. Patients treated with tacrolimus did have lower rates of 2-year disease-free survival (41% versus 51%) and overall survival (47% versus 57%) relative to patients treated with CsA; however, this was attributed to decreased survival of patients with advanced cancer–related disease. A second randomized phase III trial (n = 180) compared CsA + MTX to tacrolimus + MTX [23]. Patients receiving tacrolimus experienced a lower incidence of investigator assessed acute grade 2-4 GVHD relative to patients receiving CsA (56% versus 74%; $P = .0002$), but the risk of chronic GVHD was the same in both groups. Adverse events and the incidence of leukemia relapse were similar in both groups.

Experimental Treatments

Reduced-Intensity Conditioning Regimens. Conditioning regimens prior to bone marrow transplantation have traditionally used high-dose, myeloablative radiation and chemotherapy for maximal tumor reduction and immunosuppression in order to allow engraftment of stem cells [24]. These regimens have been associated with acute and chronic GVHD, as well as significant toxicity, which has limited its use to younger, medically fit patients [25]. Consequently, investigators are developing reduced-intensity conditioning regimens. These regimens are relatively nontoxic and nonmyeloablative, or less myeloablative, than previous regimens, thus enabling unrelated donor transplantations for older or less medically fit patients. Reduced-intensity conditioning regimens have been based on various combinations of low-dose total body irradiation (TBI), low-dose thiopental, low-dose melphalan, fludarabine, cladribine, pentostatin, and cyclophosphamide and fludarabine (Table 2 [25-33]) [25-28,34-37]. Disease control via the graft-versus-tumor effect is of utmost importance with these regimens [24]. However, older reduced-intensity conditioning regimens were associated with an incidence of grade 2-4 GVHD of 38% to 63%, whereas traditional conditioning regimens have yielded an acute GVHD incidence of 40% to 60% [25-28]. These data underscore the need for improved reduced-intensity conditioning regimens that achieve a balance between maximizing the graft-versus-tumor effect and minimizing the incidence of GVHD.

Lowsky and colleagues tested a strategy employing conditioning with anti–T-cell antibodies and repeated low-dose irradiation [29]. Patients with lymphoid malignancies or acute leukemia (n = 37) were conditioned with 10 doses of total lymphoid irradiation (80 cGy each) plus anti-thymocyte globulin (ATG). These patients were then infused with HLA-matched peripheral blood mononuclear cells from related or unrelated donors who received granulocyte colony-stimulating factor. Of 37 patients, 2 developed acute GVHD (grades 1 and 3), a markedly lower rate than that achieved by previous reduced-intensity conditioning regimens [25-28]. This regimen also demonstrated potent antitumor effects in patients with lymphoid malignancies, with 75% of patients converted from partial to complete remissions following treatment. Complete remissions were maintained in 71% of patients for at least 425 days.

Purine analogs, such as fludarabine, have played a pivotal role in the development of conditioning regimens for stem cell transplantations in patients with hematologic malignancies [24]. These agents have immunosuppressive effects that include suppression of the activity and the amounts of B-, T-, and NK cells. Although fludarabine promotes engraftment, studies have reported a significant incidence of posttransplantation infection, as well as moderate to severe GVHD. Pentostatin, another purine analog, has a unique mechanism of action that includes reversible inhibition of adenosine deaminase [38]. Because B- and T-cells are exquisitely sensitive to inhibition of adenosine deaminase, pentostatin treatment significantly reduces the number of B- and T-cells. Indeed, this drug caused significant decreases in CD4+ and CD8+ B- and T-cells in patients with pentostatin-treated hairy cell leukemia [39]. Pentostatin also inhibits overall T- and NK cell function [40]. Because pentostatin prevented acute

Table 2. Incidence of Acute and Chronic Graft-versus-Host Disease (GVHD) with Reduced-Intensity Regimens*

Study	Regimen	N	Full Donor Engraftment	Acute GVHD (grades 2-4)	Overall Survival	Chronic GVHD (all)
Slavin 1998 [26]	Flu/Bu/ATG	26	100%	38%	81%	15%
Giralt 2001 [27]	Clad/Mel	8	100%	49%	23%	68%
	Flu/Mel	78	100%			
McSweeney 2001 [28]	200 cGy TBI	45	14%	47%	55%	51%
Niederwieser 2003 [25]	Flu/TBI	52	88%	63%	25%	30% required systemic therapy
Lowsky 2005 [29]	TBI/ATG	37	Not reported	3%	72% at >222 d	22%
Kottaridis 2000 [30]	Flu/Mel/Alem	43	98%	0%	73.2% at 9 mo	2.3%
Chan 2003 [37]	ECP/Pento/TBI (MDS)	18	89%	19%	65% at 1 y	50%
Chan 2003 [31]	ECP/Pento/TBI (AML)	19	74%	21%	38% at 1 y	40%
Miller 2004 [32]	ECP/Pento/TBI	55	98%	9%	67% at 1 y	43%
Chan 2004 [33]	ECP/Pento/TBI	106	Not reported	19%	Not reported	Not reported

*Flu indicates fludarabine; Bu, busulfan; ATG, anti-thymocyte globulin; clad, cladribine; Mel, melphalan; TBI, total body irradiation; Alem, alemtuzumab; ECP, extracorporeal photopheresis; Pento, pentostatin; MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia.

GVHD in a mouse model of allogeneic bone marrow transplantation, several clinical trials have studied its safety and efficacy as a component of reduced-intensity conditioning regimens [41].

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure. The collected lymphocytes are mixed with heparin, saline, and 8-methoxypsoralen, which intercalates into the DNA of the lymphocytes, rendering these cells susceptible to apoptosis upon exposure to ultraviolet radiation. After the procedure, the lymphocytes are then returned to the patient [42,43]. Several reports have described the efficacy of a reduced-intensity conditioning regimen involving ECP, pentostatin, and TBI [31,32,44]. Patients with myelodysplastic syndrome (n = 18) were treated with a conditioning regimen consisting of ECP (days –7 and –6), pentostatin (4 mg/m^2 by continuous infusion on days –5 and –4), and TBI (600 cGy in 3 fractions on days –3 and –2) followed by allogeneic stem cell transplantation from 6/6 or 5/6 HLA-matched related donors or 6/6 HLA-matched unrelated donors. CsA and a short course of MTX were administered. Eighty-nine percent (16/18) of patients developed full donor chimerism, and there was no transplantation-related mortality by day +100. The incidence of grade 2-4 acute GVHD was 19%, whereas the incidence of extensive chronic GVHD was 18%. The 1-year failure-free and overall survival rates were 64% and 65%, respectively, at a median follow-up time of 14 months [37]. The same regimen was studied in a different cohort of 19 patients (median age, 49 years) with relapsed or refractory acute myelogenous leukemia, who were ineligible for standard allogeneic transplantation. CsA (continuous infusion), MTX (days +1 and +3), and mycophenolate mofetil (MMF, to 1 year) were administered. At a mean follow-up of 9 months, 74% of patients obtained full donor engraftment, but 5 patients died prior to engraftment due to sepsis (n = 2) or disease progression (n = 3). The incidence of grade 2-4 acute GVHD was 21% (n = 3) [31].

Subsequent clinical trials examined the efficacy of the ECP/pentostatin/low-dose TBI regimen in larger groups of patients [32]. A group of 55 patients with various malignant hematologic disorders, who were at high risk or ineligible for conventional allogeneic transplantation, were treated with the novel pentostatin-containing regimen with CsA and MTX. Full donor chimerism was achieved in 98% of the patients by day +100. The 1- and 2-year overall survival and event-free survival rates were 67%, 58%, 55%, and 47%, respectively. Grade 2-4 acute GVHD developed in 9% of patients, whereas the incidence of chronic GVHD was 43% (extensive chronic GVHD = 12%; limited GVHD = 31%). Of the engrafting patients, 72% had a complete response and 14% experienced a partial response. These results were confirmed in a cohort of 106 patients with various malignancies, who also underwent the reduced-intensity ECP/pentostatin/TBI conditioning regimen [33]. These patients received fluoroquinolone prophylaxis until neutrophil engraftment. During the first 100 days following transplantation, grade 2-4 acute GVHD occurred in 19% of patients, and 3 patients died from sepsis.

Host dendritic cells present antigens to donor T-cells, thus initiating GVHD [44]. Because the effect of conditioning regimens on dendritic cells is unknown, this was examined in 17 patients with various hematological malignancies who were undergoing stem cell transplantations. Patients underwent a traditional conditioning regimen consisting of cyclophosphamide (120 mg/kg) and TBI (1200 cGy) (n = 8) or a reduced-intensity conditioning regimen consisting of ECP (×2 days), pentostatin (8 mg/m^2 by continuous infusion for 48 hours), and TBI (600 cGy) (n = 9) followed by allogeneic stem cell transplantation from fully matched related, fully matched unrelated, or 7/8 DR-mismatched unrelated donors. Both preparative regimens decreased all 3 types of dendritic cells pretransplantation. Based on the risk factors of the study populations that were described above, the expected incidence of serious acute GVHD disease would be 40%; however, the incidence of serious acute GVHD in the reduced-intensity regimen ranged from 9% to 21% [31-33,44]. As such, the ECP/pentostatin/low-dose TBI regimen may represent a considerable improvement over previous low-dose conditioning regimens.

Experimental Drug Therapy. Sirolimus (rapamycin) is a macrolide with antifungal, antitumor, and immunosuppressive activities [45]. A phase II clinical trial studied the safety and efficacy of adding sirolimus to tacrolimus and low-dose MTX for prevention of GVHD in mismatched related donor or unrelated donor transplantation (n = 41) [46]. In this cohort, grade 0-1, 2, 3, and 4 acute GVHD occurred in 75%, 13%, 8%, and 5% of patients, respectively. The median survival was 366 days and the 1-year actuarial survival was 52%. This rate of acute GVHD in this study was low compared to historical data.

A subsequent study evaluated a sirolimus/tacrolimus combination in a MTX-free preventative regimen in a cohort of patients undergoing myeloablative allogeneic stem cell

transplantation from matched (n = 53) and unrelated (n = 30) donors [47]. The median time to neutrophil and platelet engraftment was 14 days and 12 days, respectively. The incidence of grade 2-4 and 3-4 acute GVHD was 20.5% and 4.8%, respectively, and the overall incidence of chronic GVHD was 59.1%. The authors concluded that replacement of MTX with sirolimus was associated with rapid engraftment and low incidence of acute GVHD with minimal toxicity. A later study suggested that sirolimus-based prophylaxis prevented against CMV reactivation following allogeneic hematopoeitic stem cell transplantation [48].

MMF is a selective inhibitor of the type 2 isoform of inosine monophosphate dehydrogenase, which is expressed in activated B- and T-lymphocytes [49]. A randomized trial compared CsA + MTX to CsA + MMF in a myeloablative allogeneic regimen in 6/6 matched sibling bone transplantation. Patients receiving MMF (n = 21) experienced significantly less severe mucositus than the group receiving MTX (n = 19) (21% versus 65%; $P = .008$) and the median time to neutrophil engraftment was shorter in the MMF group (11 days versus 18 days; $P < .001$). The incidence of acute GVHD was not significantly different between the treatments, but the reduced toxicity in the MMF group led to premature study closure [50]. A separate study confirmed that the MTX + CsA regimen and MMF + CsA regimen had similar efficacy in preventing acute GVHD [51].

A phase I/II trial investigated the incorporation of pentostatin into the standard tacrolimus- and MTX-containing regimen used to prevent acute GVHD in patients with leukemias and lymphomas [52]. Patients (n = 73; median age, 45 years) who received unrelated and mismatched related stem cell transplants were randomized to prophylaxis with tacrolimus and mini-MTX (control) or the same regimen with 1 of several pentostatin doses (0.5 mg/m^2, 1 mg/m^2, 1.5 mg/m^2, or 2 mg/m^2 on days 8, 15, 22, and 30 with omission of MTX on day 11). Pentostatin did not delay engraftment. The incidences of grade 2/4 and grade 3/4 acute GVHD were 47% and 20% at 0 mg/m^2, 44% and 33% at 0.5 mg/m^2, 63% and 27% at 1 mg/m^2, 29% and 10% at 1.5 mg/m^2, and 50% and 10% at 2 mg/m^2, respectively. A preliminary analysis of the data showed that pentostatin (1.5 mg/m^2) may reduce the rate of acute GVHD (probability that 1.5 mg/m^2 is better than control = 0.9341). Pentostatin did not cause a significant delay in neutrophil and platelet engraftment, nor was there a difference in the incidence of fungal, bacterial, or CMV infection/reactivation.

T-Cell Depletion. The pathophysiology of acute GVHD provides a rationale for preventative regimens that involve T-cell depletion. The ex vivo removal of T-cells from the stem cell suspension was popular in the 1980s. However, its use has declined because survival, disease-free survival, and transplantation-related mortality were not reduced compared with standard treatments in patients receiving HLA-matched grafts [19]. However, ex vivo T-cell depletion is essential in the 3 loci mismatched transplantation setting [19,53].

T-cells may also be removed using in vivo approaches. ATGs and anti-lymphocyte globulins (ALGs) have been used for many years in the hematopoietic stem cell transplantation setting. The rationale behind depleting T-cells with antibodies that are administered in vivo is reducing the host immune response, which favors engraftment and the down-regulation of donor T-cells [19,54]. Randomized clinical trials have tested the hypothesis that ALG/ATG would prevent GVHD. HLA-identical sibling transplant recipients were randomized to receive MTX alone or MTX, ALG, and prednisone. The incidence of acute GVHD was reduced in patients receiving MTX + ALG + prednisone compared to MTX (21% versus 48%, $P = .01$) [55]. A later clinical trial showed that ATG administered in the conditioning regimen of unrelated donor recipients significantly reduced the risk of developing grade 3/4 acute GVHD. However, there was a greater risk of lethal infections in patients receiving 15 mg/kg ATG [56]. When this study was updated, the results demonstrated that ATG provided significant protection against acute and chronic GVHD while shortening the time for termination of immunosuppression and improving quality of life [57].

Monoclonal Antibodies. CD25 is an activation antigen that is expressed on alloactivated T-cells, so agents targeting this receptor could potentially eliminate alloactivated T-cells without compromising engraftment. Patients received standard CSA + MTX prophylaxis with 4 infusions of anti-CD25 after stem cell transplantation from matched unrelated donors [58]. Unexpectedly, the incidence of acute GVHD was greater in the antibody-treated group (40% versus 24%) compared to matched historical controls. It is possible that the CsA blocked the induction of CD25, which have protected alloactivated T-cells while damaging CD25+ T-regulatory cells, thus permitting GVHD.

First-Line Treatment of Acute GVHD

Current Standard of Care

Corticosteroids are the current standard of care for front-line therapy of acute GVHD. In a retrospective analysis of 443 patients with acute GVHD who received steroids, the overall response rate was 55% [59]. Primary treatment generally consists of prednisone or methylprednisone (2 mg/kg per day intravenously [IV]) for 5 or 7 days. The steroid dose is then tapered in responding patients starting on day 7 [19]. A 5-day course of corticosteroids is sufficient to identify steroid-refractory acute GVHD. Nonresponders should receive second-line therapy.

Experimental Treatments

Clinical trials investigating frontline therapy for acute GVHD generally focus on adding new agents to steroid-containing treatment regimens. Clinical trials have tested the addition of ATG, various monoclonal antibodies, immunotoxins against cell surface receptors, and MMF to corticosteroids but these did not seem to offer a clear advantage [60-64]. The results obtained with ECP have been conflicting [65-67].

Recently, regimens combining steroids with daclizumab or ex vivo cultured mesenchymal stem cells (MSC) have been investigated. Daclizumab worsened 100-day survival relative to the corticosteroid-alone group, so the trial was prematurely terminated [68]. Another study tested the safety and efficacy of adding ex vivo cultured MSCs derived from unrelated donors to conventional steroid therapy in patients (n = 32) with newly diagnosed grade 2-4 acute GVHD [69]. The initial response rate was 90%; there were 19 complete responses and 7 partial responses. However, 9 (31%) patients required a second-line agent to control their disease. There were no infusional toxicities, but there was 1 case of atrial fibrillation following MSC infusion.

Second-Line Treatment of Acute GVHD

Current Standard of Care

Patients who do not respond to front-line steroid therapy are generally treated with high-dose steroids [19]. If there is a response

within 3 to 5 days, the dose is lowered to 2 mg/kg per day and the patient is treated in a manner similar to individuals who responded to low-dose steroid therapy. Potential second-line treatments include ATG, cyclosporine, tacrolimus, and MMF [70-72].

However, in studies, <60% of steroid refractory patients respond to second-line treatment [73,74]. Clearly, better treatments are needed for steroid-refractory acute GVHD.

Experimental Treatments

ECP. ECP as a component of low-intensity conditioning regimens has been used somewhat successfully for acute GVHD prophylaxis [31,37]. A phase II study evaluated the efficacy of ECP in a cohort of 21 patients with steroid-refractory acute GVHD following stem cell transplantations from siblings or unrelated donors [66]. Sixty percent of patients achieved a complete response 3 months following initiation of treatment. Complete responses were achieved in 100%, 67%, and 12% of patients with grade 2, grade 3, and grade 4 disease, respectively. At a median follow-up time of 25 months, 57% of patients were still alive. A second phase II study reported complete responses in 82% of patients with cutaneous involvement, 61% of patients with liver involvement, and 61% of patients with gut involvement. The probability of survival in complete responders was 59% compared to 11% in noncomplete responders [75].

IL-2 and TNF-Targeting Agents. Daclizumab has also been tested in the treatment of steroid-refractory acute GVHD. A phase II trial tested daclizumab in 2 cohorts of patients (n = 24, n = 19) with advanced or steroid-refractory GVHD. In the second cohort of patients, who received an additional dose of daclizumab relative to the first cohort of patients, the complete response rate on day 43 was 47% and survival on day 120 was 53% [76]. A multi-center randomized phase III clinical trial tested daclizumab in 102 patients who were being treated with methylprednisone [68]. This study was halted because the daclizumab-treated patients experienced a significantly worse 100-day survival than the control arm (77% versus 94%; $P = .02$). The 1-year overall survival was also worse in the daclizumab arm (29% versus 60%; $P = .002$). This poorer survival was attributed to relapse and infection. When patients with low-grade steroid-refractory GVHD were treated with daclizumab in a later phase II trial conducted in France (n = 62), the complete response rate was 69% with a 55% 4-year survival. A response to daclizumab was associated with fewer involved organs and a lower extent of skin involvement [77].

Infliximab is a humanized monoclonal antibody that binds to mature TNF-α and its membrane-bound precursors. Infliximab (10 mg/kg once weekly for at least 4 doses) was evaluated as a single agent in a cohort of 21 patients with steroid-refractory acute GVHD who had been receiving tacrolimus and corticosteroids [78]. The overall response rate was 67% with 13 complete responders (62%) and 5 nonresponders (24%). Overall survival was estimated to be 38%. However, 10 patients had fungal infections and 17 patients had bacterial infections. A second phase II clinical trial reported that 59% (19/32) of patients with steroid-refractory acute GVHD responded to infliximab with 6 (19%) complete responders and 13 (40%) partial responders [79]. There were infectious episodes in 72% of the patients. The use of infliximab was associated with an increased risk of non-Candida invasive fungal infections in a third cohort of patients (hazard ratio = 13.6; $P = .004$; 95% confidence interval = 2.29-80.2) [80].

Another clinical trial investigated the efficacy of daclizumab alone or in combination with infliximab/ATG in a cohort of 12 patients with steroid-refractory acute GVHD [81]. These patients received very aggressive antibacterial and aspergillus prophylaxis combined with a rapid steroid taper. This regimen produced a complete response in 100% (12/12) of the subjects, with survival rates of 100% and 73% at days 100 and 200, respectively. There was no fungal disease reported. The incidences of viral respiratory infections and CMV reactivation were 42% and 87%, respectively.

Etanercept is a soluble TNF-α receptor fusion protein that binds to soluble TNF-α, thereby preventing it from binding to and activating its cell surface receptor. A phase II clinical trial combined daclizumab and etanercept for treatment of steroid-refractory acute GVHD in a cohort of 21 patients [82]. The overall response rate was 67%. Twenty percent of patients were still alive at a median

Table 3. Therapy for Steroid-Refractory Acute Graft-versus-Host Disease (Extracorporeal Photopheresis [ECP] and Biologics)*

Study	Treatment	Phase	N	Response	Overall Survival (OS)	Adverse Event
Greinix 2000 [66]	ECP	II	21	CR: 100% grade 2, 67% grade 3, 12% grade 4	57%, 25 mo	Decreased peripheral blood counts
Greinix 2006 [75]	ECP	II	59	CR: 82% cutaneous, 61% liver, 61% gut	47%, 4 y	Not reported
Ringden 2006 [83]	MSCs	Not reported	8	CR: 75%	63%, 2 mo to 3 y	CMV gastroenteritis
Anasetti 1994 [84]	Daclizumab	I/II	20	OS: 40%, CR: 25%	Median survival 76 d	Chills, diaphoresis
Przepiorka 2000 [76]	Daclizumab	II	19	CR: 47%	53%, day 53	No serious events
Bordigoni 2006 [77]	Daclizumab	II	62	CR: 69%, PR: 90%	EFS 55%, 4 y	Infections
Lee 2004 [68]	Steroids ± daclizumab	III	102	ORR: 51% versus 53% (control)	29% versus 60% (control), 1 y	Study halted due to inferior survival
Couriel 2004 [78]	Infliximab	II	21	ORR: 67% (CR: 62%)	38%	Infections
Patriarca 2004 [79]	Infliximab	II	32	ORR: 59% (CR: 19%)	68% of responders alive at 630 d	Infections
Srinivasan 2004 [81]	Daclizumab ± Infliximab/ATG	Not reported	12	CR: 100%	73%, day 200	Bacteremia
Wolff 2005 [82]	Etanercept	II	21	ORR: 67%	20%, day 586	Infections
Shaughnessy 2005 [86]	Denileukin diftitox	II	22	CR: 41%, day 36 CR: 27%, day 100	23%, day 496	Vascular leak; hemorrhagic cystitis; thrombocytopenia; infection

*CR indicates complete response; MSCs, mesenchymal stem cells; CMV, cytomegalovirus; PR, partial response; ORR, overall response rate; ATG, anti-thymocyte globulin.

Table 4. Therapy for Steroid-Refractory Acute Graft-versus-Host Disease (Drugs)*

	Treatment	Phase	N	Response	Overall Survival	Adverse Event
Krejci 2005 [85]	MMF	II	21: 10 acute, 11 chronic	ORR: 60% acute, 64% chronic	76%, 27 mo	Infections
Takimi 2006 [88]	MMF	Not reported	11: 6 acute, 5 chronic	ORR: 67% acute, 100% chronic	64%, 18 mo	Infections
Benito 2001 [89]	Sirolimus	Not reported	21	ORR: 57% (CR: 24%)	28%, days 400-907	Myelosuppression seizure, drug discontinued (n = 10)
Bolanos-Meade 2005 [87]	Pentostatin	I	23	ORR: 78% (CR: 64%)	26% alive at end of study	Lymphopenia, neutropenia, thrombocytopenia

*MMF indicates mycophenolate mofetil; ORR, overall response rate; CR, complete response.

follow-up of 586 days. Three patients died from relapsed cancer. Mortality was caused by infectious complications (n = 11) and GVHD-related organ failure (n = 3). Chronic GVHD developed in all of the patients (n = 12) who responded to treatment and survived past day 100. Clinical trials involving ECP, MSCs, and biologic therapies are summarized in Table 3 [66,68,75-79,81-84].

Drug Therapy. The safety and efficacy of MMF was evaluated in a small clinical trial (n = 21) involving patients with steroid-refractory acute GVHD (n = 10) and chronic GVHD (n = 11) [85]. MMF (2 g daily) was added to the steroid regimen, which was tapered. The overall response rate was 62%; the response rates in acute GVHD and chronic GVHD were 60% and 64%, respectively. The most frequent adverse event was infectious complications. Denileukin diftitox is an IL-2 diphtheria toxin fusion protein that was tested in a phase II clinical trial involving 22 patients with steroid-resistant acute GVHD [86]. The complete response rates on days 36 and 100 were 41% and 27%, respectively. The median survival was 121 days for all patients, and 5 patients were still alive at a median of 496 days. Of these 5 patients, 4 had responded to denileukin diftitox by day 36, and the other survivor responded to salvage therapy. The higher dose level (9.0 μg/kg on days 1-5, then weekly on days 8, 15, 22, and 29) was associated with significant toxicity (vascular leak syndrome and vancomycin-resistant enterococcus sepsis) and had to be discontinued, whereas the lower dose (4.5 μg/kg on days 1-5, then weekly on days 8, 15, 22, and 29) was better tolerated. Adverse events included mild vascular leaks (n = 2), hemorrhagic cystitis (n = 2), acute respiratory distress syndrome (n = 1), grade 3 thrombocytopenia (n = 5), and severe infection (n = 7).

Pentostatin has shown promise as a component of prophylactic regimens for acute GVHD [31,37,52]. A phase I, dose escalation study examined the safety of pentostatin for treatment of patients with steroid-refractory acute GVHD [87]. These patients (n = 23) had biopsy-confirmed grade 2-4 acute GVHD following an allogeneic bone marrow transplantation or donor lymphocyte infusion. Pentostatin was administered IV for 3 days at 1 mg/m^2 per day, 2 mg/m^2 per day, 3 mg/m^2 per day, and 4 mg/m^2 per day. The dose-limiting toxicity was the presence of infections at the 2-mg/m^2 dose level. All of the patients experienced lymphopenia. Other toxicities included grade 1 neutropenia (n = 1), grade 3 thrombocytopenia (n = 1), and grade 1 transaminase elevation. Based on this study, the recommended dose for subsequent evaluation is 1.5 mg/m^2 per day IV × 3 days.

Twenty-two patients were assessed for a response to pentostatin [87]. The complete and partial response rates were 64% (n = 14) and 14% (n = 3), respectively. Three patients (13%) had progressive disease. When retreated for progression, 100% of patients (6/6) responded. The median survival for all patients was 85 days. Six patients (26%) were still alive at the end of the study and 1 of these patients developed chronic GVHD. The authors concluded that pentostatin has promising activity for the treatment of steroid-refractory acute GVHD and that a second course of pentostatin is feasible and beneficial. Clinical trials involving drugs are summarized in Table 4 [85,87-89].

CHRONIC GVHD

Incidence/Symptoms/Grading

Chronic GVHD, which develops in about 50% of patients receiving allogeneic stem cell transplants, is a potentially life-threatening complication of this procedure [90]. The incidence of chronic GVHD is increasing due to increased age of transplant recipients, increased survivorship, and the use of peripheral blood stem cells. The 5-year survival rate for poor prognosis disease is 40%. Chronic GVHD usually manifests 3 to 7 months following a transplantation.

Chronic GVHD usually affects the eyes, skin, oral cavity, lungs, liver, gastrointestinal tract, kidneys and the heart [91,92]. Symptoms include rash, diarrhea, mucositis, transaminase elevation, and bronchiolitis with organizing pneumonia. The National Institutes of Health Chronic GVHD Consensus Project has proposed a diagnosis and staging system that separately scores the degree of involvement of individual organs on a scale of 0 to 3 (0 = asymptomatic, 3 = the most extensive involvement) [93].

Pathogenesis

The preponderance of evidence suggests that donor T-cells play an important role in the development of chronic GVHD. Although donor lymphocyte infusion can induce cancer remission in some patients with relapsed leukemia, this procedure is associated with the development of chronic GVHD [94,95]. Likewise, depletion of donor T-cells from the graft prevents acute and chronic GVHD, but increases the risk of relapse [96]. The targets for attack may be host non-HLA antigens, such as minor histocompatibility antigens [7]. Because chronic GVHD mimics many autoimmune diseases, the involvement of humeral immunity is inferred. Indeed, a coordinated B- and T-cell immune response to an H-Y antigen was demonstrated in 1 patient with chronic GVHD that developed following an allogeneic stem cell transplantation [97]. Data also support a role for host dendritic cells in the development of chronic GVHD [98]. Many studies show a relationship between the development of GVHD and a positive graft-versus-tumor effect [7,99]. These observations underscore the need for balancing treatment of GVHD while maintaining a graft-versus-tumor effect.

Table 5. Therapy for Steroid-Refractory Chronic Graft-versus-Host Disease (Extracorporeal Photopheresis and Biologics)*

	Treatment	Phase	N	Response	Overall Survival	Adverse Event
Couriel 2006 [107]	Extracorporeal photopheresis	Retrospective	71	ORR: 61% (CR: 20%)	41%, 34 mo	Abdominal pain, blood pressure, fever, required transfusions
Cutler 2006 [108]	Rituximab	I/II	21	ORR: 70%	100%, 15 mo	Infections

*ORR indicates overall response rate; CR, complete response.

Prevention of Chronic GVHD

Current Standard of Care

Because the pathophysiology of chronic GVHD is not well understood, prophylactic regimens are limited [7]. The development of acute GVHD appears to be an important risk factor for chronic GVHD, so efforts have focused on the prophylaxis of acute GVHD. Although reduced-intensity transplantations are associated with a reduced risk of acute GVHD, this is not the case with chronic GVHD [100,101]. Likewise, the extended use of cyclosporine for prophylaxis did not effect the incidence of chronic GVHD [21,102]. When thalidomide was added to a CsA and MTX prophylaxis regimen, the incidence of chronic GVHD increased with a concurrent decrease in survival [103]. However, the addition of ATG to CsA/MTX provided protection against extensive chronic GVHD and chronic lung dysfunction in a cohort of patients (n = 109) who underwent unrelated donor transplantation [57].

First-Line Treatment of Chronic GVHD

Current Standard of Care

Corticosteroids are the most effective agents for the treatment of chronic GVHD. The addition of CsA to a standard prednisone-containing regimen was examined in a large, randomized clinical trial (n = 307) involving patients with chronic GVHD having platelet counts >100,000/μL [104]. The hazards of transplantation-related and overall mortality, recurrent malignancy, secondary therapy, and discontinuation of immunosuppressive therapy were not significantly different in the CsA/prednisone group compared to the prednisone-only group. However, survival without a recurrence of cancer was lower in the CsA-containing arm. The incidence of avascular necrosis was lower in the CsA/prednisone group than the prednisone-only group (13% versus 22%, respectively; $P = .04$). The addition of tacrolimus to a steroid-containing regimen yielded a high response rate (72%), but was associated with high chronic GVHD-related mortality (34%) and a significant need for salvage therapy (47%) [105].

Second-Line Treatment of Chronic GVHD

Current Standard of Care

There is no standard of care for refractory chronic GVHD. Therapy generally consists of long-term administration of corticosteroids in conjunction with other immunosuppressive agents [7]. MMF is the most commonly used agent for the treatment of steroid-refractory chronic GVHD. Clinical trials involving this agent have relied on very small groups of patients. The largest study consisted of a retrospective analysis of the efficacy of MMF in first-line (n = 10) and second-line (n = 24) treatment of chronic GVHD [106]. When MMF was added to standard CsA, tacrolimus, and/or prednisone, the response rates in first-line and second-line settings were 90% and 75%, respectively. Eighty-five percent of patients were still alive at a median follow-up of 24 months, but 3 patients had to discontinue the drug due to abdominal cramps. There were 12 infectious episodes. The authors concluded that MMF had a steroid-sparing effect and did not seem to increase the rate of infections or relapse.

Experimental Therapy

ECP. Although ECP has been tested in small groups of patients, these studies are difficult to interpret due to differences in diagnostic and response criteria and in treatment schedules [107]. A recent retrospective study evaluated the efficacy of ECP in a large cohort of patients (n = 71) with severe steroid-refractory chronic GVHD. The response rate was 61% (n = 43) with 14 complete responses. The best responses were in the skin (59%), liver (71%), eye (67%), and oral cavity (77%). The incidence of steroid discontinuation at 1 year was 22%. At a median follow-up time of 34 months, 59% of patients had died. Five-year overall survival was 19%. Infection (n = 28; 67%) and relapse (n = 12; 29%) were the primary causes of death.

Monoclonal Antibodies. The CD20 antibody rituximab was evaluated in a cohort of 21 patients with steroid-refractory chronic GVHD [108]. The clinical response rate was 70% with 2 patients achieving complete remission. Responses were limited to patients with musculoskeletal and cutaneous disease, and were durable through 1 year after initiation of therapy. The use of rituximab allowed for a 75% reduction in the dose of prednisone. Rituximab was well tolerated and toxicity was limited to infectious complications. Clinical trials involving ECP and monoclonal antibodies are summarized in Table 5 [107,108].

Table 6. Therapy for Steroid-Refractory Chronic Graft-Versus-Host Disease (Drugs) *

	Treatment	Phase	N	Response	Overall Survival	Adverse Event
Akpek 2001 [109]	High-dose pulse steroids	Not reported	61	48% major response	88%, 1 y; 81%, 2 y	Hypertension, tachycardia, infections; otherwise well tolerated
Mookerjee 1999 [111]	MMF + tacrolimus	Retrospective	26	46%	Not reported	Gastrointestinal
Johnston 2005 [110]	Sirolimus-calcineurin inhibitor	II	19	63% in patients tolerating drug	89%, end of trial	>30% grade 3/4, early termination
Gilman 2000 [114]	Hydroxy-chloroquine	II	40	CR: 1%; PR: 44%	75% responders, 32 mo; 40% nonresponders, 30 mo	Gastrointestinal infections
Bolanos-Meade 2005 [112]	Pentostatin	II	42	ORR: 50% (CR: 12%)	64%	Infections
Jacobsohn 2004 [113]	Pentostatin	II (pediatric subset from above)	16	ORR: 81%	Not reported	Elevated creatinine

*MMF indicates mycophenolate mofetil; CR, complete response; PR, partial response; ORR, overall response rate.

Drug-Based Therapy. Phase I/II studies have evaluated high-dose pulse steroids, tacrolimus/MMF, and sirolimus for the second-line treatment of chronic GVHD [109-111]. When 61 patients with severe refractory chronic GVHD were treated with high-dose pulse steroids (10 mg/kg per day for 4 days followed by tapering), the major response rate was 48% and the probability of survival at 1 year and 2 years was 88% and 81%, respectively [109]. MMF and tacrolimus were well tolerated and produced an objective response rate of 46% in 26 patients with refractory chronic GVHD [111]. The combination of sirolimus, calcineurin inhibitors, and prednisone was tested in a phase II study involving 19 patients with chronic GVHD [110]. Sirolimus was discontinued in 9 patients due to poor compliance (n = 1), patient request (n = 1), or an adverse event (n = 7). This study was terminated early due to >30% of the patients experiencing grade 3/4 toxicities. Although 94% (15/16) of evaluable patients had a clinical response, sirolimus was withdrawn from 5 of these patients due to toxicity yielding a response rate of 63% (10/16) in patients tolerating the drug.

A recent clinical trial tested the efficacy and safety of pentostatin (4 mg/m^2 IV every 2 weeks for 6 months) in a cohort of 52 patients (median age, 40.5 years; range, 5-67 years) with refractory chronic GVHD, who failed at least 2 prior immunosuppressive regimens [112]. Patients received very aggressive infection prophylaxis including steroid tapering, antibiotics, antifungals, and antivirals. Amongst the 42 evaluable patients, there were 5 complete responses, 16 partial responses, and 5 mixed responses, yielding an overall response rate of 50%. Therapy was well tolerated with infectious complications being the most prominent adverse event. Fifteen patients died; causes of death included mucormycosis, pneumonia, disseminated fungal infection, fungal pneumonia, and progressive disease.

Using a patient subset from the above clinical trial [139], the efficacy of pentostatin was analyzed in 16 patients <20 years of age [113]. Patients who failed at least 2 prior immunosuppressive regimens were treated with pentostatin (4 mg/m^2 IV every 2 weeks for 6 months). There were 5 complete responses and 8 major responses, yielding an overall response rate of 81%. Of 11 patients who received prednisone treatment, 73% (n = 8) were completely weaned from the drug or were able to receive less than 25% of the original dose. Therapy was well tolerated with one probable pentostatin toxicity event (elevated creatinine) requiring withdrawal of the patient. There were no severe infections, and there were 2 deaths that were both GVHD related. These results show that pentostatin has considerable clinical activity in adults and children/adolescents. Table 6 summarizes ongoing clinical trials [109-114].

CONCLUSIONS

Acute and chronic GVHD cause a significant amount of mortality and morbidity following allogeneic hematopoietic stem cell transplantation. Consequently, improved prophylactic and treatment regimens are needed to combat these disorders. New regimens are being rationally designed to target key processes and molecules that are involved in the initiation, propagation, and maintenance of acute GVHD. However, significant challenges remain, including achieving a better understanding of the pathogenesis of chronic GVHD and controlling infections related to immunosuppression. Additionally, the development of effective prophylactic and treatment regimens for acute and chronic GVHD that maintain the beneficial graft-versus-tumor effect is of paramount importance. Although many obstacles remain, there have already been significant advances in the understanding, prevention, and treatment of acute and chronic GVHD.

REFERENCES

1. Margolis J, Vogelsang G. An old drug for a new disease: pentostatin (Nipent) in acute graft-versus-host disease. *Semin Oncol*. 2000;27:72-77.
2. Lazarus HM, Vogelsang GB, Rowe JM. Prevention and treatment of acute graft-versus-host disease: the old and the new. A report from the Eastern Cooperative Oncology Group (ECOG). *Bone Marrow Transplant*. 1997;19:577-600.
3. Gratwohl A, Hermans J, Apperley J, et al. Acute graft-versus-host disease: grade and outcome in patients with chronic myelogenous leukemia. Working Party Chronic Leukemia of the European Group for Blood and Marrow Transplantation. *Blood*. 1995;86:813-818.
4. Nash RA, Pepe MS, Storb R, et al. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood*. 1992;80:1838-1845.
5. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
6. Nevo S, Enger C, Swan V, et al. Acute bleeding after allogeneic bone marrow transplantation: association with graft versus host disease and effect on survival. *Transplantation*. 1999;67:681-689.
7. Cutler C, Antin JH. Chronic graft-versus-host disease. *Curr Opin Oncol*. 2006;18:126-131.
8. Childs RW. Allogeneic stem cell transplantation. In: Devita VTJ, Hellman S, Rosenberg SA, eds. Vol. *Cancer Principles and Practice of Oncology*. Philadelphia, PA: Lippincott-Raven Publishers, 2001:2779-2798.
9. Aschan J, Ringden O. Prognostic factors for long-term survival in leukemic marrow recipients with special emphasis on age and prophylaxis for graft-versus-host disease. *Clin Transplant*. 1994;8:258-270.
10. Champlin R. Hematopoietic cellular transplantation In: Kufe DW, Pollock RE, Weichselbaum RR, et al, eds. *Cancer Medicine*. Hamilton, Ontario: BC Decker Inc, 2003:1019-1036.
11. Bolanos-Meade J. Update on the management of acute graft-versus-host disease. *Curr Opin Oncol*. 2006;18:120-125.
12. Antin JH, Ferrara JL. Cytokine dysregulation and acute graft-versus-host disease. *Blood*. 1992;80:2964-2968.
13. Ferrara JL, Levy R, Chao NJ. Pathophysiologic mechanisms of acute graft-vs.-host disease. *Biol Blood Marrow Transplant*. 1999;5:347-356.
14. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood*. 1990;76:1867-1871.
15. Hill GR, Crawford JM, Cooke KR, et al. Total body irradiation and acute graft-versus-host disease: the role of gastrointestinal damage and inflammatory cytokines. *Blood*. 1997;90:3204-3213.
16. Li XC, Strom TB, Turka LA, et al. T cell death and transplantation tolerance. *Immunity*. 2001;14:407-416.
17. Ferrara JL, Guillen FJ, van Dijken PJ, et al. Evidence that large granular lymphocytes of donor origin mediate acute graft-versus-host disease. *Transplantation*. 1989;47:50-54.
18. Ghayur T, Seemayer TA, Kongshavn PA, et al. Graft-versus-host reactions in the beige mouse. An investigation of the role of host and donor natural killer cells in the pathogenesis of graft-versus-host disease. *Transplantation*. 1987;44:261-267.
19. Bacigalupo A. Management of acute graft-versus-host disease. *Br J Haematol*. 2007;137:87-98.
20. Zikos P, Van Lint MT, Frassoni F, et al. Low transplant mortality in allogeneic bone marrow transplantation for acute myeloid leukemia: a randomized study of low-dose cyclosporin versus low-dose cyclosporin and low-dose methotrexate. *Blood*. 1998;91:3503-3508.
21. Bacigalupo A, Van Lint MT, Occhini D, et al. Increased risk of leukemia relapse with high-dose cyclosporine A after allogeneic marrow transplantation for acute leukemia. *Blood*. 1991;77:1423-1428.
22. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood*. 1998;92:2303-2314.
23. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood*. 2000;96:2062-2068.
24. Foss FM. The role of purine analogues in low-intensity regimens with allogeneic hematopoietic stem cell transplantation. *Semin Hematol*. 2006;43:S35-S43.
25. Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and fludarabine

followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood*. 2003;101:1620-1629.
26. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood*. 1998;91:756-763.
27. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood*. 2001;97:631-637.
28. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood*. 2001;97:3390-3400.
29. Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med*. 2005;353:1321-1331.
30. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. *Blood*. 2000;96:2419-2425.
31. Chan GW, Foss FM, Klein AK, et al. Extracorporeal photopheresis, pentostatin and total body irradiation reduced intensity transplantation in relapsed or refractory AML patients: evidence for early graft versus tumor effect with less GVHD. *Blood*. 2003;102. Abstract 3265.
32. Miller KB, Roberts TF, Chan G, et al. A novel reduced intensity regimen for allogeneic hematopoietic stem cell transplantation associated with a reduced incidence of graft-versus-host disease. *Bone Marrow Transplant*. 2004;33:881-889.
33. Chan GW, Relias V, Klein AK, et al. Even coagulase negative staphyloccus infections following reduced intensity transplantation are associated with increased transplant complications and poorer overall survival. *Biol Blood Marrow Transplant*. 2004;104:208a. Abstract 214.
34. Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol*. 1998;16:2817-2824.
35. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. *N Engl J Med*. 1986;314:729-735.
36. Kottaridis PD, Chakraverty R, Milligan DW, et al. A non-myeloablative regimen for allogeneic stem cell transplantation with a low incidence of GVHD. *Bone Marrow Transplantation*. 2000;25:S26.
37. Chan GW, Foss FM, Klein AK, et al. Reduced-intensity transplantation for patients with myelodysplastic syndrome achieves durable remission with less graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9:753-759.
38. Saven A, Piro L. Newer purine analogues for the treatment of hairy-cell leukemia. *N Engl J Med* 1994;330:691-697.
39. Seymour JF, Talpaz M, Kurzrock R. Response duration and recovery of CD4+ lymphocytes following deoxycoformycin in interferon-alpha-resistant hairy cell leukemia: 7-year follow-up. *Leukemia*. 1997;11:42-47.
40. Urba WJ, Baseler MW, Kopp WC, et al. Deoxycoformycin-induced immunosuppression in patients with hairy cell leukemia. *Blood*. 1989;73:38-46.
41. Epstein J, Bealmear PM, Kennedy DW, et al. Prevention of graft-versus-host disease in allogeneic bone marrow transplantation by pretreatment with 2'-deoxycoformycin. *Exp Hematol*. 1986;14:845-849.
42. Fimiani M, Di Renzo M, Rubegni P. Mechanism of action of extracorporeal photochemotherapy in chronic graft-versus-host disease. *Br J Dermatol*. 2004;150:1055-1060.
43. Alcindor T, Gorgun G, Miller KB, et al. Immunomodulatory effects of extracorporeal photochemotherapy in patients with extensive chronic graft-versus-host disease. *Blood*. 2001;98:1622-1625.
44. Chan GW, Betancur M, Sprague KA, et al. Effects of preparative regimens on host dendritic cells pre-transplant in allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007;13:125. Abstract 344.
45. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc*. 2003;35:7S-14S.
46. Antin JH, Kim HT, Cutler C, et al. Sirolimus, tacrolimus, and low-dose methotrexate for graft-versus-host disease prophylaxis in mismatched related donor or unrelated donor transplantation. *Blood*. 2003;102:1601-1605.
47. Cutler C, Li S, Ho VT, et al. Extended follow-up of methotrexate-free immunosuppression using sirolimus and tacrolimus in related and unrelated donor peripheral blood stem cell transplantation. *Blood*. 2006.
48. Marty FM, Bryar J, Browne SK, et al. Sirolimus-based graft-versus-host disease prophylaxis protects against cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation: a cohort analysis. *Blood*. 2007.
49. Allison AC, Eugui EM. Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). *Clin Transplant*. 1996;10:77-84.
50. Bolwell B, Sobecks R, Pohlman B, et al. A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2004;34:621-625.
51. Nash RA, Johnston L, Parker P, et al. A phase I/II study of mycophenolate mofetil in combination with cyclosporine for prophylaxis of acute graft-versus-host disease after myeloablative conditioning and allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2005;11:495-505.
52. de Lima M, Couriel D, Munsell M, et al. Pentostatin, tacrolimus, and "mini"-methotrexate for graft-versus-host disease (GVHD) prophylaxis: a phase I/II controlled, randomized study. *ASH Annual Meeting Abstracts*. 2004;104. Abstract 727.
53. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. *N Engl J Med*. 1998;339:1186-1193.
54. Byrne JL, Stainer C, Cull G, et al. The effect of the serotherapy regimen used and the marrow cell dose received on rejection, graft-versus-host disease and outcome following unrelated donor bone marrow transplantation for leukaemia. *Bone Marrow Transplant*. 2000;25:411-417.
55. Ramsay NK, Kersey JH, Robison LL, et al. A randomized study of the prevention of acute graft-versus-host disease. *N Engl J Med*. 1982;306:392-397.
56. Bacigalupo A, Lamparelli T, Bruzzi P, et al. Antithymocyte globulin for graft-versus-host disease prophylaxis in transplants from unrelated donors: 2 randomized studies from Gruppo Italiano Trapianti Midollo Osseo (GITMO). *Blood*. 2001;98:2942-2947.
57. Bacigalupo A, Lamparelli T, Barisione G, et al. Thymoglobulin prevents chronic graft-versus-host disease, chronic lung dysfunction, and late transplant-related mortality: long-term follow-up of a randomized trial in patients undergoing unrelated donor transplantation. *Biol Blood Marrow Transplant.* 2006;12:560-565.
58. Martin PJ, Pei J, Gooley T, et al. Evaluation of a CD25-specific immunotoxin for prevention of graft-versus-host disease after unrelated marrow transplantation. *Biol Blood Marrow Transplant*. 2004;10:552-560.
59. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant*. 2002;8:387-394.
60. Wetzig T, Sticherling M, Simon JC, et al. Medium dose long-wavelength ultraviolet A (UVA1) phototherapy for the treatment of acute and chronic graft-versus-host disease of the skin. *Bone Marrow Transplant*. 2005;35:515-519.
61. Doney KC, Weiden PL, Storb R, et al. Treatment of graft-versus-host disease in human allogeneic marrow graft recipients: a randomized trial comparing antithymocyte globulin and corticosteroids. *Am J Hematol*. 1981;11:1-8.
62. Gratama JW, Jansen J, Lipovich RA, et al. Treatment of acute graft-versus-host disease with monoclonal antibody OKT3. Clinical results and effect on circulating T lymphocytes. *Transplantation*. 1984;38:469-474.
63. Martin PJ, Nelson BJ, Appelbaum FR, et al. Evaluation of a CD5-specific immunotoxin for treatment of acute graft-versus-host disease after allogeneic marrow transplantation. *Blood*. 1996;88:824-830.
64. Basara N, Blau WI, Romer E, et al. Mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant patients. *Bone Marrow Transplant*. 1998;22:61-65.
65. Smith EP, Sniecinski I, Dagis AC, et al. Extracorporeal photochemotherapy for treatment of drug-resistant graft-vs.-host disease. *Biol Blood Marrow Transplant*. 1998;4:27-37.
66. Greinix HT, Volc-Platzer B, Kalhs P, et al. Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study. *Blood*. 2000;96:2426-2431.
67. Besnier DP, Chabannes D, Mahe B, et al.

Treatment of graft-versus-host disease by extracorporeal photochemotherapy: a pilot study. *Transplantation*. 1997;64:49-54.
68. Lee SJ, Zahrieh D, Agura E, et al. Effect of upfront daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood*. 2004;104:1559-1564.
69. Kebriaei P, Isola L, Bahceci E, et al. Phase II trial of Prochymal™ (ex-vivo cultured adult human mesenchymal stem cells) and corticosteroids as primary treatment for acute graft-vs-host disease (aGVHD). *ASH Annual Meeting Abstracts*. 2006;108. Abstract 3231.
70. Mollee P, Morton AJ, Irving I, et al. Combination therapy with tacrolimus and anti-thymocyte globulin for the treatment of steroid-resistant acute graft-versus-host disease developing during cyclosporine prophylaxis. *Br J Haematol*. 2001;113:217-223.
71. Couriel D, Caldera H, Champlin R, et al. Acute graft-versus-host disease: pathophysiology, clinical manifestations, and management. *Cancer*. 2004;101:1936-1946.
72. Van Lint MT, Milone G, Leotta S, et al. Treatment of acute graft-versus-host disease with prednisolone: significant survival advantage for day +5 responders and no advantage for nonresponders receiving anti-thymocyte globulin. *Blood*. 2006;107:4177-4181.
73. Weisdorf D, Haake R, Blazar B, et al. Treatment of moderate/severe acute graft-versus-host disease after allogeneic bone marrow transplantation: an analysis of clinical risk features and outcome. *Blood*. 1990;75:1024-1030.
74. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: secondary treatment. *Blood*. 1991;77:1821-1828.
75. Greinix HT, Knobler RM, Worel N, et al. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica*. 2006;91:405-408.
76. Przepiorka D, Kernan NA, Ippoliti C, et al. Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. *Blood*. 2000;95:83-89.
77. Bordigoni P, Dimicoli S, Clement L, et al. Daclizumab, an efficient treatment for steroid-refractory acute graft-versus-host disease. *Br J Haematol*. 2006;135:382-385.
78. Couriel D, Saliba R, Hicks K, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. *Blood*. 2004;104:649-654.
79. Patriarca F, Sperotto A, Damiani D, et al. Infliximab treatment for steroid-refractory acute graft-versus-host disease. *Haematologica*. 2004;89:1352-1359.
80. Marty FM, Lee SJ, Fahey MM, et al. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. *Blood*. 2003;102:2768-2776.
81. Srinivasan R, Chakrabarti S, Walsh T, et al. Improved survival in steroid-refractory acute graft versus host disease after non-myeloablative allogeneic transplantation using a daclizumab-based strategy with comprehensive infection prophylaxis. *Br J Haematol*. 2004;124:777-786.
82. Wolff D, Roessler V, Steiner B, et al. Treatment of steroid-resistant acute graft-versus-host disease with daclizumab and etanercept. *Bone Marrow Transplant*. 2005;35:1003-1010.
83. Ringden O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation*. 2006;81:1390-1397.
84. Anasetti C, Hansen JA, Waldmann TA, et al. Treatment of acute graft-versus-host disease with humanized anti-Tac: an antibody that binds to the interleukin-2 receptor. *Blood*. 1994;84:1320-1327.
85. Krejci M, Doubek M, Buchler T, et al. Mycophenolate mofetil for the treatment of acute and chronic steroid-refractory graft-versus-host disease. *Ann Hematol*. 2005;84:681-685.
86. Shaughnessy PJ, Bachier C, Grimley M, et al. Denileukin diftitox for the treatment of steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:188-193.
87. Bolanos-Meade J, Jacobsohn DA, Margolis J, et al. Pentostatin in steroid-refractory acute graft-versus-host disease. *J Clin Oncol*. 2005;23:2661-2668.
88. Takami A, Mochizuki K, Okumura H, et al. Mycophenolate mofetil is effective and well tolerated in the treatment of refractory acute and chronic graft-versus-host disease. *Int J Hematol*. 2006;83:80-85.
89. Benito AI, Furlong T, Martin PJ, et al. Sirolimus (rapamycin) for the treatment of steroid-refractory acute graft-versus-host disease. *Transplantation*. 2001;72:1924-1929.
90. Baird K, Pavletic SZ. Chronic graft versus host disease. *Curr Opin Hematol*. 2006;13:426-435.
91. Srinivasan R, Balow JE, Sabnis S, et al. Nephrotic syndrome: an under-recognised immune-mediated complication of non-myeloablative allogeneic haematopoietic cell transplantation. *Br J Haematol*. 2005;131:74-79.
92. Rackley C, Schultz KR, Goldman FD, et al. Cardiac manifestations of graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:773-780.
93. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945-956.
94. Guglielmi C, Arcese W, Dazzi F, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. *Blood*. 2002;100:397-405.
95. Porter DL, Collins RH, Jr., Hardy C, et al. Treatment of relapsed leukemia after unrelated donor marrow transplantation with unrelated donor leukocyte infusions. *Blood*. 2000;95:1214-1221.
96. Ho VT, Soiffer RJ. The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation. *Blood*. 2001;98:3192-3204.
97. Zorn E, Miklos DB, Floyd BH, et al. Minor histocompatibility antigen DBY elicits a coordinated B and T cell response after allogeneic stem cell transplantation. *J Exp Med*. 2004;199:1133-1142.
98. Chan GW, Gorgun G, Miller KB, et al. Persistence of host dendritic cells after transplantation is associated with graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9:170-176.
99. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. *Blood*. 2005;105:2973-2978.
100. Shlomchik WD, Lee SJ, Couriel D, et al. Transplantation's greatest challenges: advances in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007;13:2-10.
101. Mielcarek M, Martin PJ, Leisenring W, et al. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood*. 2003;102:756-762.
102. Storb R, Leisenring W, Anasetti C, et al. Methotrexate and cyclosporine for graft-vs.-host disease prevention: what length of therapy with cyclosporine? *Biol Blood Marrow Transplant*. 1997;3:194-201.
103. Chao NJ, Parker PM, Niland JC, et al. Paradoxical effect of thalidomide prophylaxis on chronic graft-vs.-host disease. *Biol Blood Marrow Transplant*. 1996;2:86-92.
104. Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood*. 2002;100:48-51.
105. De Jesus J, Ghosh S, Hsu Y, et al. Tacrolimus in combination with steroids for the treatment of chronic GvHD. *Biol Blood Marrow Transplant*. 2004;10(suppl 1):49-50.
106. Lopez F, Parker P, Nademanee A, et al. Efficacy of mycophenolate mofetil in the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:307-313.
107. Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. *Blood*. 2006;107:3074-3080.
108. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood*. 2006;108:756-762.
109. Akpek G, Lee SM, Anders V, et al. A high-dose pulse steroid regimen for controlling active chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2001;7:495-502.
110. Johnston LJ, Brown J, Shizuru JA, et al. Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:47-55.
111. Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. *Bone Marrow Transplant*. 1999;24:517-520.
112. Bolanos-Meade J, Jacobsohn D, Anders V, et al. Pentostatin in steroid-refractory chronic graft-versus-host disease. *ASH Annual Meeting Abstracts*. 2005;106:1805-.
113. Jacobsohn DA, Browning B, Thormann K, et al. Pentostatin: efficacy in refractory chronic GVHD in children. *ASH Annual Meeting Abstracts*. 2004;104. Abstract 2249.
114. Gilman AL, Chan KW, Mogul A, et al. Hydroxychloroquine for the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2000;6:327-334.

Current Advances in the Treatment of Acute and Chronic Graft-versus-Host Disease

CME Assessment Test

1. **Acute graft-versus-host disease (GVHD) is graded using the Keystone criteria.**
   A. True
   B. False

2. **Traditional high-dose myeloablative conditioning regimens are associated with:**
   A. A high incidence of acute GVHD
   B. A high incidence of chronic GVHD
   C. Significant toxicity
   D. All of the above
   E. None of the above

3. **The following purine analog(s) have been used in pretransplantation conditioning regimens:**
   A. Fludarabine
   B. Alemtuzumab
   C. Pentostatin
   D. A and B
   E. A and C

4. **An incidence rate of ___ for acute GVHD is associated with reduced-intensity conditioning regimens involving extracorporeal photopheresis/pentostatin and total body irradiation, compared with an incidence rate of 40% to 60% with cyclophosphamide-based conditioning regimens.**
   A. 0% to 9%
   B. 9% to 21%
   C. 21% to 40%
   D. 40% to 60%

5. **Chronic GVHD develops in approximately ___ of patients receiving allogeneic stem cell transplants.**
   A. 5%
   B. 10%
   C. 20%
   D. 50%
   E. 100%

6. **The incidence of chronic GVHD is increasing due to:**
   A. Increasing age of transplant recipients
   B. Increasing survivorship
   C. Peripheral blood stem cells
   D. All of the above
   E. None of the above

7. **Reduced-intensity transplantations are associated with a reduced risk of chronic GVHD.**
   A. True
   B. False

8. **There is no current standard of care for steroid-refractory chronic GVHD.**
   A. True
   B. False

9. **The following drug(s) is/are being evaluated for the treatment of steroid-refractory chronic GVHD:**
   A. Chloroquine
   B. Ranitidine
   C. Pentostatin
   D. A and B
   E. B and C
   F. A and C

10. **A phase II clinical trial evaluated pentostatin in patients with chronic GVHD who failed at least 2 prior immunosuppressive regimens. The overall response rate in this group of patients was:**
    A. 7%
    B. 19%
    C. 50%
    D. 81%

CME Assessment Test Answer Sheet – Program ID #07160

Release Date: August 31, 2007 **Last Review Date: August 31, 2007** **Expiration Date: August 31, 2008**

Instructions

(1) Read the articles in the publication carefully. (2) Circle the correct response to each question on the Answer Sheet. (3) Complete the Evaluation Form. (4) To receive CME credit, fax the completed Answer Sheet and Evaluation Form to the Office of Continuing and Professional Education (414-456-6623) or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. No processing fee is required.

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2.	A	B	C	D	E	**6.**	A	B	C	D	E	**10.**	A	B	C	D						
3.	A	B	C	D	E	**7.**	A	B														
4.	A	B	C	D		**8.**	A	B														

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