ASBMT
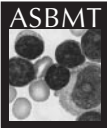American Society for Blood and Marrow Transplantation

Introduction
The Conundrum of Chronic Graft-versus-Host Disease
by John R. Wingard, MD
Editor

What can be done about chronic graft-versus-host disease (GVHD)? Strategies that completely eradicate it rob much of the curative powers of allogeneic hematopoietic cell transplantation (HCT). Left uncontrolled, it is a source of considerable morbidity and represents the major cause of death in HCT survivors. Clearly, the challenge is the happy median: not too much, not too little; or, better yet, dissect out the mediators of antitumor activity ("the good guys") for preservation and enrichment, while eliminating "the bad guys" that cause normal tissue injury in the transplant recipient.

In this issue, the proceedings of a satellite symposium presented at the Tandem BMT meetings in 2001 present a discussion of the problems that chronic GVHD poses and the therapeutic advances that have been made and their limitations, and discuss the preliminary results of several therapeutics that offer promise in improving control of the deleterious effects of chronic GVHD. Sadly, as noted, today's therapies were defined more than a decade ago. Why haven't we made progress since? Clearly, the reasons are multiple. First is a practical one: at onset of chronic GVHD many of the patients have returned to their local communities, making enrollment into clinical trials as well as monitoring the course of investigational therapies difficult. Second, the endpoints of treatment have been difficult to define and standardize across centers and make concrete enough to convince regulatory bodies that a new therapy is an advance over currently available therapies. Third, we need new more effective and safer therapeutic options. Clearly, there are good prospects as discussed in this symposium. A partnership between clinical investigators, the biotech industry, and regulatory agencies is needed for us to move forward.

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Be a part of a national organization established to promote
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PRELIMINARY APPLICATION

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 marrow 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.

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

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ASBMT News

Dr. John Wingard Installed as ASBMT President; Dr. Armand Keating Elected Vice President

John R. Wingard, MD, director of the Bone Marrow Transplant Program at the University of Florida College of Medicine in Gainesville, has been installed as president of the American Society for Blood and Marrow Transplantation (ASBMT).

Armand Keating, MD, professor of medicine and director of the Division of Hematology at the University of Toronto, Ontario, Canada, is the newly elected vice president, to become president in 2004. Dr. Keating also is head of the Department of Medical Oncology and Hematology at Princess Margaret Hospital/Ontario Cancer Institute, and director of the Division of Hematology-Oncology at Mount Sinai Hospital, Toronto.

The installation of officers and directors occurred at the ASBMT Annual Meeting in Orlando.

Newly elected and installed directors are:

- **James L. M. Ferrara, MD**, University of Michigan Cancer Center, Ann Arbor.
- **Robert Negrin, MD**, Stanford University Hospital, Stanford, Calif.
- **Robert M. Rifkin, MD**, Rocky Mountain Blood and Marrow Transplant Team, Denver.

Joseph H. Antin, MD, chief of the Bone Marrow Transplant Team at the Dana-Farber Cancer Institute, Boston, was elevated to president-elect, and will assume the presidency in 2003.

The new ASBMT president, Dr. Wingard, is a professor of medicine and pediatrics, and an associate director for clinical and translational research at the University of Florida's Shand's Cancer Center in Gainesville.

He received a bachelor of arts degree from Yale University and his medical degree at The Johns Hopkins University School of Medicine. His residency was at the University of Tennessee Center for Health Sciences, and he completed a fellowship in medical oncology at Johns Hopkins, where he remained on the faculty for 14 years. In

1991 he accepted an appointment as director of the Bone Marrow Transplant Program at Emory University in Atlanta.

Dr. Wingard's research interests include infections in stem cell transplantation, graft-versus-host disease, and quality of life and psychosocial adjustment of patients after transplantation.

He is the primary or co-author of more than 200 research articles, 225 abstracts, and 25 book chapters and is the editor of two books. He is the editor of *Blood and Marrow Transplantation Reviews*, and serves on the editorial boards of *Biology of Blood and Marrow Transplantation* and *Transplant Infectious Disease*.

BMT*net* Provides New Portal to BMT Resources on the World Wide Web

BMT*net* is a new portal to blood and marrow transplantation resources on the World Wide Web.

The portal, or doorway, with links to multiple Web sites, is a joint project of seven blood and marrow transplantation organizations, supported by an unrestricted educational grant from Pharmacia Corporation. It was introduced at the Tandem BMT Meetings in February in Orlando.

At a single web address– **www.bmtnet.org** –healthcare professionals, patients and the general public can find blood and marrow transplantation information and easily move back and forth among the Web sites of the seven participating organizations:

- American Society for Blood and Marrow Transplantation (ASBMT)
- Canadian Blood and Marrow Transplant Group (CBMTG)
- European Group for Blood and Marrow Transplantation (EBMT)
- Foundation for Accreditation of Cellular Therapy (FACT)
- International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Marrow Transplant Registry (ABMTR)
- International Society for Cellular Therapy (ISCT)

- National Marrow Donor Program (NMDP)

In addition to direct access to the seven Web sites, BMT*net* provides links to a directory of blood and marrow transplantation centers, relevant meetings and conferences, periodicals in the BMT field, continuing education opportunities and other Web sites of interest.

The original concept for BMT*net* was created by ASBMT and IBMTR/ABMTR and, for the past three years, BBMT*net* has served as a joint portal to their two Web sites. Now, with the assistance of the grant from Pharmacia Corporation, the portal has been expanded to encompass the seven participating organizations.

ASBMT Launches Web-Based "Job Connection"

ASBMT has launched the "Job Connection," a new online marketplace for those seeking or offering employment in the BMT field.

Accessed through the Society's home page, the Job Connection visitors can search for positions, post their resumes or advertise job openings. The Job Connection includes all categories of BMT employment: physicians, investigators, laboratory technicians, nurses and administrators.

Much like classified want ads in a newspaper or journal, the employment listings can be searched free of charge by job seekers, and there is a nominal fee for those announcing positions to fill. The fee can be paid online by credit card.

The Job Connection can be accessed from the Society's home page at **www. asbmt.org**.

ASBMT also continues to offer display advertising of employment opportunities in its monthly journal, *Biology of Blood and Marrow Transplantation*. To advertise a position in the journal, call (434) 817-2000 and ask for David Ern at Extension 135.
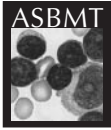
SYMPOSIUM Report

Emerging Strategies in the Treatment of Chronic Graft-versus-Host Disease
February 15, 2001, Keystone, Colorado

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Michael Bishop, MD
Introduction

Graft-versus-host disease (GVHD) is a complex immunologic response mounted by donor tissue on transplantation into a recipient host. Occurring after allogeneic blood or bone marrow transplantation, GVHD possesses a high morbidity and mortality rate, with chronic GVHD (cGVHD) contributing to roughly 54% of non–relapse-related deaths associated with transplantations [1]. Estimates from the International Bone Marrow Transplant Registry (IBMTR) indicate that 8,000 allogeneic hematopoietic stem cell transplantations (HSCTs) are done annually in the United States [2]. Given the number of allogeneic HSCTs performed in this country and the high mortality rate that can occur with ensuing cGVHD, clinicians are faced with the challenge of improving the overall survival rates of their transplantation patients.

Data reported by the Late Effects Working Committee of the IBMTR indicate that excluding relapse-related death, HSCT patients who survived disease-free for 2 years posttransplantation succumbed to cGVHD on average about 54% of the time, regardless of the initial hematologic cancer that resulted in a HSCT. Despite deaths occurring from new cancers, infections, organ failure, and other unknown causes, cGVHD remained the most significant cause of death among the 375 individuals followed [1]. More-over, a series of studies citing cGVHD incidence rates reports that cGVHD was noted among 25% to 65% of transplant recipients, as follows: unrelated donor HSCT, 55% incidence of cGVHD [3]; cord blood stem cell transplantation (BSCT), 25% [4]; donor lymphocyte infusion (DLI), 61% [5]; and nonmyeloablative HSCT, 65% [6]. It is of importance to note that Collins et al also reported that cGVHD occurred in more than 80% of the DLI patients who responded to treatment, a correlation that was clinically and statistically significant ($P < .00001$) [5]. Furthermore, among the nonmyeloablative SCT patients, cGVHD incidence could be viewed as excessively high among this group of patients; however, this population of patients was older (median age, 55 years) and had more advanced disease at the study outset [6]. Coupling these findings with the >50% overall mortality rate cited above emphasizes the need for improved GVHD treatments.

In a recent randomized, comparative trial that evaluated the use of allogeneic bone marrow (BM) versus allogeneic peripheral blood stem cells for BM rescue among 172 hematologic cancer patients, promising findings were presented [7]. Bensinger et al reported no significant differences for the incidence of either acute GVHD (aGVHD) or cGVHD. Moreover, the number of deaths from GVHD of either type was equal in both treatment groups (n = 3) [7]. Although survival was not an endpoint of this study, relative to BM, peripheral blood cells more rapidly restored blood counts among those treated, occurring with no greater an incidence in GVHD as well [7]. Although these results are encouraging, larger, randomized studies are necessary to fully validate these results.

Risk Factors for cGVHD

Regardless of BM or BSCT, many risk factors exist that can predispose patients to cGVHD. These include:
- prior aGVHD
- older donor/recipient age
- HLA mismatch
- use of an unrelated donor
- viral infection (eg, cytomegalovirus)
- splenectomy
- DLI
- use of blood as a source of stem cells

And, despite continued research, the clinical treatment of cGVHD has remained fairly constant. Today's treatment approaches for cGVHD are largely based on the 1988 report by Sullivan et al, in which alternating-day cyclosporine (CsA) and prednisone (PDN) were evaluated among 61 patients with extensive cGVHD [8]. CsA was given at 6 mg/kg doses bid and PDN was given at 2 mg/kg per day for 1 week, after which time both drugs were given on alternating days. The prednisone dose was subsequently tapered over the following 4 weeks to 1 mg/kg per day and maintained until 9 months posttransplantation. At 9 months posttransplantation,

Table 1. Potential Complications Associated with Steroid-Based cGVHD Treatment

• Cataracts	• Myopathy
• Headaches	• Avascular necrosis
• Mood swings	• Venous fragility
• Hypertension	• Swelling/edema
• Gastritis	• Thinning of the skin
• Hyperglycemia	• Increased catabolism
• Adrenal suppression	• Fever suppression
• Adipose redistribution	• Immune suppression
• Osteopenia	

17/61 (28%) had a complete response; 20 of 61 (33%) had a partial response; 8 of 61 (13%) exhibited progressive disease; and 16 of 61 (26%) died or relapsed before 9 months posttransplantation. Importantly, hypertension, renal insufficiency, and various infections were the most commonly occurring side effects of treatment.

Treatments Limited by Side Effects and Subjective Grading

Despite the apparent success of treatment cited by Sullivan and colleagues, steroid-based treatment regimens for cGVHD remain problematic. As shown in Table 1, HSCT patients are likely to experience a plethora of side effects. Importantly, the need to balance clinical utility against clinical risk remains a central aspect of treatment selection and use among patients at risk for cGVHD. However, current treatments, no matter how effective, are associated with a high degree of complications.

Because preexisting disease plays an integral role in the natural history of cGVHD and also influences treatment outcome, accurately characterizing cGVHD is critical for improving patient care. Although clinical grading systems are used for GVHD (Table 2) [9], subjective interpretation of these guidelines can lead to clinically inappropriate classifications of patients. The differences between "mild" and "moderate" disease fall in a gray area that could result in different clinicians stratifying these patients quite differently when treatments are selected. Moreover, additional ambiguity lies in the difficulty of accurately identifying the number of organ systems involved with GVHD, further complicating the evaluation and classification of cGVHD patients.

Treatment Endpoints Key for Robust Trials and Successful Outcomes

Emerging treatments and refined disease grading systems will undoubtedly improve outcomes. However, endpoints such as treatment response, infections and complications, quality of life and performance status, relapse potential and failure-free survival cannot be overlooked. Each of these so-called endpoints weighs heavily in the decision-making process for or against specific treatment approaches. The continued balance between risk and benefit is ever-present. Yet, given these endpoints, overall survival remains the principal endpoint against which all others are judged. It is the charge of the clinician to strive for improving disease-free survival among the cGVHD patients, while simultaneously mitigating the severity of the remaining endpoints. The gold standard for such improvements lies in the controlled clinical trial; designing well-balanced studies that target these crucial

Table 2. Clinical Grading System for cGVHD [9]

cGVHD Description	Type
Progressive	Direct extension of aGVHD
Quiescent	Occurs following resolution of aGVHD
De novo	Occurs in the absence of aGVHD
	Severity
Limited	Mild involvement of ≥2 organ systems
Extensive	Moderate to severe involvement of ≥2 organ systems

endpoints is the first step toward improving survival for cGVHD patients. This symposium presents an overview of current treatments for cGVHD along with encouraging new data on emerging therapeutic modalities. Within the context of successful cGVHD patient management, these therapies are expected to improve outcomes and extend survival.

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Mary E. D. Flowers, MD
Traditional Treatment of Chronic Graft-versus-Host Disease

Chronic graft-versus-host disease (GVHD) is a major late complication after allogeneic hematopoietic transplantation (HST), occurring in approximately 50% of patients between 3 and 24 months after transplantation [1,2]. The number of chronic GVHD cases are on the rise as a result of increasing numbers of older transplant recipients, peripheral blood stem cells as the source of HST, use of mismatched and unrelated donors, and treatment with donor lymphocyte infusion for recurrent malignancy after HST [1-6].

Chronic GVHD resembles several collagen vascular diseases, usually of the skin, mouth, eyes, liver, gastrointestinal tract, female genitalia, and fascia. The lungs and the muscles may also be affected by chronic GVHD. Weight loss and immunodeficiency are hallmarks of disease severity. The clinical manifestation and morbidity of chronic GVHD vary according to the numbers of sites (limited versus extensive) and the severity of the abnormality involving each site [3-5]. Extensive chronic GVHD is a major determinant factor in late morbidity and mortality after allogeneic HST [5] and, if untreated, fewer than 20% of patients survive without disability at 4 years after transplantation [7].
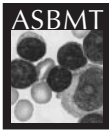
Early Treatment Intervention Is Key

Initial studies reported by Sullivan et al indicated that treatment with corticosteroids alone used late in the course of chronic GVHD resulted in a 23% survival probability at 3 years after transplantation [7] compared to 76% if treatment was administered earlier in the course of the disease [8]. Earlier results of combination therapy with azathioprine (AZA) and prednisone (PDN) found a survival of 65% to 90% at 3 years after transplantation when this therapy was used either for early treatment of chronic GVHD or for failure of initial treatment with PDN alone [7]. These initial findings suggested that early treatment of chronic GVHD and combination therapy with PDN and AZA might improve survival in patients with extensive chronic GVHD.

Outcome Depends on Platelet Count and Progressive Onset of Chronic GVHD

In a multivariate analysis, thrombocytopenia (platelet count <100,000/mm^3) at the time of diagnosis of chronic GVHD and progressive onset from acute to chronic GVHD have been identified as independent risk factors for poor outcome in patients with chronic GVHD [8,9]. Patients with chronic GVHD with thrombocytopenia or progressive onset of chronic GVHD have an unfavorable outcome compared to patients without thrombocytopenia and without progressive onset chronic GVHD.

Treatment of Chronic GVHD with Corticosteroids— Historical Perspective

Results of PDN Alone or Combined with AZA

The effect of PDN plus placebo was compared to PDN plus AZA treatment combination in a randomized, placebo-controlled, phase III prospective study in patients with extensive chronic GVHD with platelet counts ≥100,000/mm^3 at the time of diagnosis [8]. Survival at 5 years after transplantation was higher for patients treated in the randomized study with PDN plus placebo compared to that for patients treated with PDN plus AZA combination

Table 1. Characteristics of Patients Treated with Cyclosporine and Prednisone as Primary Treatment for Extensive Chronic GVHD According to Risk Features* at Time of Diagnosis

Characteristics	Standard Risk, N = 126 n (%)	High Risk, N = 111 n (%)
Age at transplantation, median (range)	32 (2-57)	32 (1-60)
Type of onset		
Progressive	0 (0)	64 (58)
Quiescent	82 (65)	31 (28)
De novo	44 (35)	16 (14)
Donor type		
Matched related	87 (69)	56 (50)
Mismatched related	23 (18)	30 (27)
Unrelated	16 (13)	25 (23)
Disease Risk at Transplantation†		
Low	46 (37)	33 (30)
Intermediate	45 (36)	44 (40)
High	35 (28)	34 (31)
Patient/Donor Sex		
F/F	39 (31)	22 (20)
F/M	22 (17)	24 (22)
M/F	30 (24)	32 (29)
M/M	35 (28)	33 (30)
Chronic GVHD onset day		
< day 100	23 (18)	69 (62)
≥ day 100	103 (82)	42 (38)

Risk categories: High: < 100,000/mm^3 platelet count at diagnosis or progressive onset; Standard: ≥ 100,000/mm^3 platelet count at diagnosis and quiescent or de novo onset.

†*Disease risk categories: Low: CML-CP, refractory anemia, AA, blackfan; Intermediate: CML-AP, CML-BC in remission, acute leukemia in remission, lymphoma in remission, RAEB, MDS (NOS), CLL, PNH; High: CML-BC, JCML, acute leukemia in relapse or de novo, lymphoma in relapse, RAEBT, myeloma.*

(61% versus 47%, respectively) (P = .03). The nonrelapse mortality rate was worst for patients treated with PDN plus AZA (40%) compared to that for patients given PDN plus placebo (21%) (P = .003). Results of this study revealed that treatment with PDN plus AZA combination for chronic GVHD without thrombocytopenia was inferior to treatment with PDN alone.

Results of PDN Alone or Combined with Cyclosporine

The effect of PDN alone was studied prospectively for early treatment of extensive chronic GVHD in patients with platelet count <100,000/mm^3 at time of diagnosis of GVHD [8]. Survival was only 26% for patients treated with PDN alone in this prospective study compared to 61% for patients without thrombocytopenia treated with PDN and placebo in the parallel randomized trial (P < .001) [8]. Results of this study suggested that PDN alone used early in the treatment of chronic GVHD in patients with thrombocytopenia had little effect in improving survival. These studies were the first to identify platelet count <100,000/mm^3 as a risk factor associated with a poor survival in patients with chronic GVHD.

The effect of cyclosporine (CsA) treatment in extensive chronic GVHD was first studied in a prospective study in patients with thrombocytopenia as a marker of "high risk" disease [10]. In this first study, treatment with a combination of CsA and alternating-day PDN resulted in a 51% survival at 4 years after transplantation. The alternating-day PDN regimen in this study aimed at reducing toxicity related to long-term corticosteroids. The survival rate was significantly higher in this study than the 26% rate previously reported for a similar patient population treated with PDN alone [8]. These earlier results with CsA and PDN combination prompted a subsequent randomized, prospective phase III trial to study the efficacy of CsA compared to CsA plus alternating-day PDN combination as primary treatment of extensive chronic GVHD in patients with platelet count <100,000 /mm^3. Unfortunately, comparison of outcome between the 2 treatment arms was impaired, because the majority of patients randomized to the CsA-alone arm were already receiving this therapy for prevention or treatment of acute GVHD at the time of the study enrollment. For patients treated in the 2-drugs arm in this randomized study, the 5-year survival probability
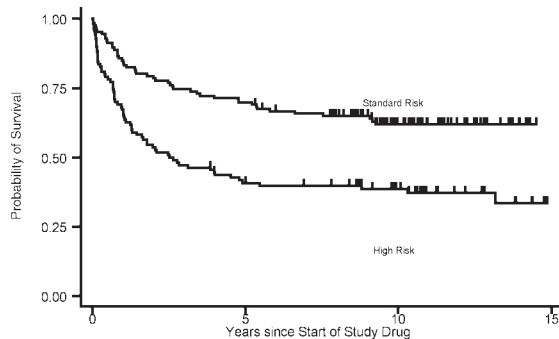
Figure 1. Probability of survival in patients with extensive chronic graft-versus-host disease treated with cyclosporine and prednisone. Lower curve indicates patients with high-risk features (ie, <100,000/mm³ platelet count or progressive onset). Upper curve indicates patients with standard-risk features (ie, ≥100,000/mm³ platelet count and without progressive onset).

was 40%, compared to 26% reported earlier with PDN alone in patients with thrombocytopenia [8].

Primary Treatment with PDN and CsA Combination in Patients with and without Thrombocytopenia or Progressive Onset of Chronic GVHD—Update Results

CsA and alternating-day PDN have been used as a mainstay of treatment for patients with extensive chronic GVHD with platelet count <100,000/mm³ or progressive onset chronic GVHD ("high risk") and for patients without thrombocytopenia and without progressive onset of chronic GVHD ("standard risk"). We carried out a recent analysis of patients with standard- and high-risk features of chronic GVHD treated with CsA and alternating-day PDN combination as primary treatment for extensive chronic GVHD as part of 2 randomized studies in Seattle between 1985 and 1989. The study included 126 standard-risk patients and 111 high-risk patients. Table 1 displays characteristics of all patients according to risk features. Survival at 10 years was superior for patients with standard-risk features compared to high-risk patients (62% versus 39%, respectively) (Figure 1). Table 2 displays the results of this study. As expected, the nonrelapse mortality rate was higher for patients in the high-risk group (39%) compared to the standard-risk patients (21%) (P = .001). Approximately 40% of patients

with high-risk features were able to discontinue treatment with all systemic immunosuppressive (IS) medications during the first 5 years after treatment was started (Figure 2). For the standard-risk group, approximately 60% of patients were able to discontinue treatment with all systemic IS medications during the first 5 years after treatment was started (Figure 3). The probability of relapse or death during IS therapy at 5 years was approximately 55% in the high-risk group and approximately 30% for the standard-risk group (Figures 2 and 3). Results of this recent analysis indicate that treatment outcome of CsA and PDN combination as primary therapy of chronic GVHD differs significantly according to the presence or absence of thrombocytopenia at time of diagnosis of chronic GVHD and progressive onset of chronic

GVHD. Lower survival rates, higher nonrelapse mortality rates, and longer duration of systemic IS medications were observed in patients with high-risk features of chronic GVHD compared to patients with standard risk. These results also indicate that significant improvement in the treatment of chronic GVHD is needed, especially for patients with thrombocytopenia, progressive onset, and other features such as >50% skin involvement, recently identified as a risk factor for a poor outcome in chronic GVHD [11].

Treatment Challenges

Clinicians are faced with a myriad of challenges, many of which are founded in the poorly understood pathophysiology of chronic GVHD. Among these challenges are the complexity of the disease process, the variability of currently available staging systems, and the difficulty in quantifying changes in GVHD patients over time. In addition, over the last one and a half decades, changes in the eligibility profiles of transplantation patients, increased use of peripheral blood as a source of stem cells, and the selection of transplant donors other than HLA-identical siblings are other factors that need to be considered when designing and analyzing results of future clinical trials.

Summary

It is estimated that there are approximately 4000 annual new cases of chronic GVHD worldwide. Because the disease

Table 2. Results of Combination Cyclosporine and Prednisone as Primary Treatment for Extensive Chronic GVHD According to Risk Features at Time of Diagnosis*

Outcome	Standard Risk, N = 126	High Risk, N = 111
Number of patients alive	79	41
Years of follow-up amongst living patients, median (range)	10.5 (5.3-14.5)	10.8 (3.9-14.8)
No. of patients dying	47 (37%)	70 (63%)
Years to death among dying patients, median (range)	1.4 (0.02-9.3)	0.9 (0.0-13.2)
No. of patients relapsing	27 (21%)	33 (30%)
Years to death among relapsing patients, median (range)	0.8 (0.02-6.3)	0.6 (0.1-3.7)
No. of patients experiencing a nonrelapse death	26 (21%)	39 (35%)
Years to nonrelapse death, median (range)	1.6 (0.04-9.3)	0.7 (0.0-13.1)
No. of patients successfully stopping all IS†	78 (62%)	45 (41%)
Years to stopping IS, median (range)	1.6 (0.3-8.2)	1.3 (0.6-6.8)
No. of patients dying or relapsing while on IS	43 (34%)	63 (57%)
Years to death or relapse while on IS, median (range)	0.8 (0.02-6.3)	0.6 (0.0-8.8)

IS indicates immunosuppressive medications.
†Successfully stopping all IS medications without systemic IS requirements thereafter.

High Risk

Figure 2. Probability of discontinuation of all systemic immunosuppressive (IS) medications (lower curve) and probability of death or relapse during IS therapy (upper curve) in patients with high-risk chronic graft-versus-host disease (ie, <100,000/mm³ platelet count or progressive onset).
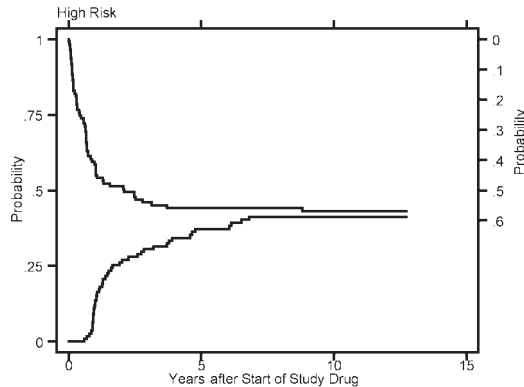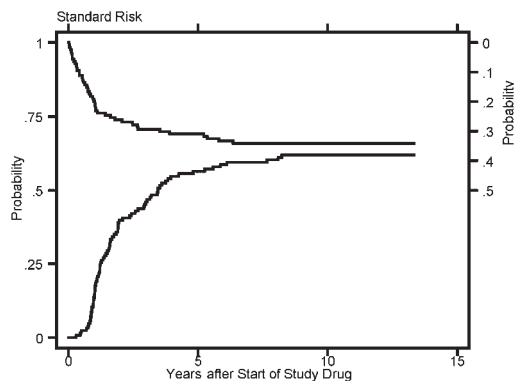
Standard Risk

Figure 3. Probability of discontinuation of all systemic immunosuppressive (IS) medications (lower curve) and probability of death or relapse during IS therapy (upper curve) in patients with standard risk features of chronic graft-versus-host-disease (ie, ≥100,000/mm³ platelet count and without progressive onset).

can plague patients for years, even decades, its long-term ramifications are costly in terms of health care utilization and debilitating in terms of quality of life

and, ultimately, survival. Conventional therapies with corticosteroids have offered a reasonable starting point in treating chronic GVHD but are clearly associated

with high morbidity (ie, avascular necrosis, diabetes, hypertension, sleep disturbance, mood sings, infections, osteoporosis, cataracts, change in body habitus, cutaneous atrophy and striae, and inhibition in growth and development in children). Future improvement in treatment strategies, including new IS medications, new antibody-based modalities, and ex vivo interventions, such as extracorporeal photopheresis, are currently under investigation. The success of new therapies will depend on several factors including lower toxicity profile compared to current treatments, better control of disease manifestation, and improvement of quality of life of patients with chronic GVHD, while not compromising disease-free survival mediated by graft-versus-tumor effect.

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Francine M. Foss, MD
Emerging Therapies for Chronic Graft-versus-Host Disease

Chronic GVHD remains a significant cause of morbidity and mortality after bone marrow transplantation (BMT), with death most often resulting from infection and less often [1] from pulmonary failure or autoimmune complications. Primary

therapy for cGVHD includes corticosteroids and cyclosporine A (CsA). Other immunosuppressive agents, including azathioprine and mycophenolic acid, have demonstrated limited efficacy. Novel strategies to target alloreactive effector T-cells include use of the nucleoside analog, pentostatin, as well as monoclonal antibodies and the interleukin-2 receptor fusion toxin,

Ontak (Ligand Pharmaceuticals, San Diego, CA) [2-5]. Phototherapy (PUVA) has been used to alleviate the symptoms of chronic skin GVHD but has no effect on visceral involvement [6-9]. Recently, extracorporeal photopheresis has demonstrated efficacy in both acute and chronic GVHD as well as in solid organ rejection after renal and cardiac allografts [10-12].

Pentostatin

Pentostatin is a purine nucleoside analog that binds to and inhibits the enzyme adenosine deaminase and is cytotoxic for T-lymphocytes [13-14]. Doses of 2 to 5 mg/m² per day ×3 days have demonstrated efficacy in patients with hairy cell leukemia and B- and T-cell lymphomas [13-15]. Lymphopenia is induced in most of the treated patients with repeated dosing. Other toxicities include infection, renal dysfunction, and, rarely, neurotoxicity [14].

Because of their effects on T-lymphocytes, which are purported to play a role in ongoing tissue damage in GVHD, the role of pentostatin and other nucleoside analogs for prevention or palliation of GVHD is worthy of further investigation [16]. Experimentally, pentostatin has been shown to decrease both the number and function of CD4+ and CD8+ T-cells by lowering IL-2 production and diminishing the proliferation of T-cells in response to IL-2. In addition, pentostatin has been shown to decrease the number and function of NK cells [16].

A recent study by Margolis et al demonstrated an overall response rate of 75% with pentostatin administered at a low dose of 0.125 to 2 mg/m² per day for 3 days in 12 patients with steroid-refractory aGVHD [13]. In this study, all patients failed to respond to conventional immunosuppressive therapies, including high-dose (2.5 mg/kg) steroids, antithymocyte globulin (ATG), daclizumab, infliximab, and mycophenolate mofetil (MMF), and all patients had grades II to IV aGVHD. Overall, 5 patients (42%) had a complete response (CR) and 4 patients (33%) exhibited partial responses (PR; 75% overall response rate). Although 80% of grade III and 29% of grade IV patients responded to pentostatin treatment, the overall mortality rate was 75%, with 50% mortality at day 45 (Table 1). These results demonstrate activity of pentostatin in aGVHD, but optimal dose levels and dosing schedules remain to be determined [13]. A larger phase II study is now underway, utilizing pentostatin at a dosage of 4 mg/m² every other week for 24 weeks in patients with refractory aGVHD.

Table 1. Response to Various Treatments for GVHD

Extracorporeal photopheresis (ECP)	
Foss et al	
No. patients with steroid refractory cGVHD	7
Age range, y	25-59
Time after transplantation of ECP initiation, d	101-600
No. of cycles	5 to 28
Response	
Partial response	5
No change	2
Decreased immunosuppressive drugs	6Yes, 1No
Pentostatin	
Margolis et al [13]	
No. patients with steroid refractory aGVHD	12
Age range	6 mo-50 y
Dose, mg/m² per day	0.125-2
Response	
Complete response	5
Partial response	4
45-d survival, %	50
Foss et al	
No. patients having undergone aGVDH prophylaxis	21
Age range, y	23-70
Dose, mg/m²	8
Preparative ECP administered	Yes
Reduced total body irradiation administered	Yes
Response rate, as d-30 full donor engraftment, %	90
Remission rate, %	79
Interleukin-2 receptor–targeted therapies	
Przepiorka et al [4]	
No. patients with advanced/refractory aGVHD	43
Age range, y	1-53
Daclizumab dose, mg/kg iv	1
Overall response rate, %	51
Overall 120-day survival, %	40

The use of pentostatin as a prophylactic agent has recently been explored in a pilot study at New England Medical Center (Table 1). Twenty-one patients with a median age of 51 years (range, 23-70 years) were treated with a preparative regimen consisting of extracorporeal photopheresis on days –6 and –5; continuous infusion pentostatin at a dose of 8 mg/m² given over 48 hours on days –4 and –3; and reduced dose TBI (rTBI) consisting of 600 cGy TBI on days –2 and –1, followed by allogeneic bone marrow infusion on day 0. Prophylaxis for aGVHD included CsA at a dose of 2.5 mg/kg IV starting on day –1 and methotrexate on days 1 and 5. All patients were high risk, based on age over 50 years, history of prior transplantation, mismatched or unrelated donors, hepatitis B, renal failure, secondary acute myelogenous leukemia, or cardiopulmonary compromise.

Full donor engraftment occurred in 90% of patients by day 30. Of significance, the incidence of grades II to IV aGVHD in this high-risk group of patients was less than 10% and compares favorably with the expected incidence of 40% based on studies using other conditioning regimens in comparable risk groups. The regimen was well tolerated and led to full donor engraftment in 81% of patients and disease remission in 79%. To determine whether extracorporeal photopheresis (ECP) in the preparative regimen was responsible for the low incidence of GVHD, a follow-up study randomizing between ECP/pentostatin/rTBI and pentostatin/rTBI is planned.

IL-2 Receptor Targeted Therapies

The interleukin-2 receptor is a heterotrimeric complex consisting of the p55, p75, and p64 subunits. High-affinity IL2R (p55,75,p64) is present on activated T-lymphocytes and is critically involved in T-cell proliferation and activation by IL-2 [17,18]. Daclizumab (humanized anti-Tac, HAT) is a human monoclonal IgG1 antibody directed against the p55 or IL2R α subunit [17,18]. Daclizumab has demonstrated activity in renal allograft rejection by diminishing T-cell activation and in selected patients with T-cell leukemia at doses up to 1.5 mg/kg [19].

In clinical trials with daclizumab in patients with advanced or refractory aGVHD, Przepiorka et al reported response rates of 29% to 47% [4]. Among 43 patients treated at a dose of 1 mg/kg, an overall response rate of 30% was observed in patients with grades III to IV. Organ-specific complete responses were 54% for skin, 37% for gut, and 17% for liver. The 120-day survival ranged from 29% to 53% [4].

Alternate targeted approaches include the use of immunotoxins and fusion toxins directed at IL2R-expressing lymphocytes. Conjugates of single chain anti-TAC antibody conjugated to pseudomonas exotoxin have demonstrated activity in hematologic malignancies [20]. Ontak, a recombinant fusion toxin, has demonstrated clinical efficacy in patients with CD25 expressing B- and T-cell lymphomas [21]. Ontak is composed of the human IL-2 gene fused to a truncated, enzymatically active portion of the diphtheria toxin gene [20]. The recombinant protein targets both high- and intermediate-affinity IL-2R–expressing cells and inhibits protein synthesis by ADP ribosylation of elongation factor 2. Ontak has demonstrated efficacy in patients with IL2R-expressing non-Hodgkin's lymphomas and cutaneous T-cell lymphoma. In patients with these diseases, transient modulation of circulating populations of $CD4^+CD25^+$ and $CD8^+CD25^+$ normal lymphocytes was observed, suggesting that Ontak was capable of targeting normal activated lymphocytes and might therefore be useful in T-cell–mediated disorders.

Two ongoing pilot studies are evaluating the use of Ontak in both aGVHD and cGVHD. In a phase I study conducted at Dana Farber Cancer Institute and at New England Medical Center, Ontak was administered at a dose of 9 μg/kg per day given 1, 2, or 3 days per week for 4 weeks in patients with refractory aGVHD (Table 1). The dose was escalated to 18 μg/kg per day in the last cohort. At the time of this writing, responses had been observed in the first cohort, and treatment had been well tolerated without significant toxicity.

Extracorporeal Photopheresis

ECP is an immunotherapeutic modality that has demonstrated clinical efficacy in cutaneous T-cell lymphoma/Sezary syndrome (CTCL), scleroderma, and other autoimmune disorders. ECP involves extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen (8-MOP), followed by reinfusion of the treated cells. 8-MOP is a naturally occurring furocourarin that is biologically inert unless exposed to UVA light, when it becomes photoactivated and covalently binds and cross-links DNA, leading to initiation of apoptosis.

During a single treatment cycle of ECP, approximately 240 cc of buffy coat and 300 mL of plasma are collected into a buffy coat bag from 6 collection cycles. The cells are exposed to UVA at 1-2 joules/cm² per cell beginning immediately after the first cells are collected [21]. Examination of the cells after UVA exposure and prior to reinfusion demonstrates that about 2% to 5% of the total circulating peripheral blood mononuclear cells undergo apoptosis [22]. An intravenous formulation of 8-MOP, Uvadex (Therakos, Exton, PA), allows for direct instillation of the photosensitizing agent into the collected plasma and buffy coat ex vivo prior to UVA exposure.

Edelson et al reported the first use of ECP in the treatment of cutaneous T-cell lymphoma (CTCL) [23]. In these studies with orally administered 8-MOP, 73% of patients with refractory CTCL responded, with a 64% decrease in skin involvement after 22 ± 10 weeks. Subsequent studies have confirmed these results and have demonstrated that response is correlated with the presence of circulating T-leukemia cells and that responding patients demonstrate an increase in $CD8^+$ cytotoxic T-cells. The mechanism of action of ECP in CTCL is believed to be related to an autoimmunization phenomenon [24-26]. Circulating tumor cells undergo apoptosis in the presence of UVA and methoxypsoralen; at the same time, circulating monocytes differentiate and are capable of phagocytosing the apoptosing tumor cells and processing

tumor antigens, which are then expressed in the context of MHC antigens.

The effects of UVA irradiation of effector lymphocytes has been explored in the context of autoimmune disorders and bone marrow transplantation models. In these studies, the administration of 8-MOP and UVA-irradiated spleen and bone marrow cells to mice receiving allografts resulted in a significant attenuation of GVHD compared to littermates who received non–UVA-irradiated cells [27]. In another study, using (C57BL/6 × DBA/2)F1 (B6D2F1) mice which, when inoculated with parental DBA/2 (D2) splenocytes, develop chronic stimulatory graft-versus-host reaction with clinical features of systemic lupus erythematosis, injection of UVA/8-MOP–treated D2 splenocytes was capable of attenuating the effects of GVHD that had been initiated by prior injection of D2 cells to initiate lupus-like disease [28].

Although the immunomodulatory effects of ECP are believed to be related to a direct effect of the treatment to induce apoptosis in circulating leukemia cells, the mechanism of action is unclear in autoimmune disorders and in GVHD. We initiated a study to evaluate the biomodulatory effects of ECP in patients with steroid refractory cGVHD who were treated with ECP for 2 consecutive days every 2 weeks [29]. The median time from BMT in our population was 667 days (range, 101-600 days). Overall, 7 of 10 patients had a clinical response to ECP, with improvement in skin GVHD in 7, ocular involvement in 5 of 7, oral GVHD in 5 of 8, and hepatic enzymes in 2 of 3. Immunosuppressive therapy was decreased or discontinued in 7 of 10 patients. In contrast to reports by Child et al, who noted a lower response rate in patients who initiated ECP late in the course of cGVHD [30], 4 of 5 patients starting ECP therapy more than 10 months after BMT responded.

Immunomodulatory effects of ECP are shown for 7 patients in Table 1. In these patients there was a normalization of the CD4/CD8 ratios, an increase in

NK populations, and an overall decrease in the number of dendritic cells after ECP. In all responding patients, a 50% or greater decrease in circulating CD80^{+} and CD123^{+} dendritic cell populations was noted with no marked change in CD28 expression on lymphocytes, suggesting no effect of ECP to modulate class I major histocompatibility complex-restricted T-cell function. The decrease in antigen-presenting cells paralleling a decrease in CD8^{+} cells suggested an overall suppression of alloreactivity. Further studies demonstrated a significant attenuation of dendritic cell function as measured by proliferation of allogeneic and autologous lymphocytes in a mixed lymphocyte reaction, suggesting a direct effect of UVA exposure on circulating dendritic cells.

Supporting earlier reports, our studies demonstrated that UVA exposure in mice inhibits both the number and function of dendritic Langerhans cells in the skin, resulting in immune tolerance to allogeneic skin grafts [31]. The importance of antigen-presenting cells in the initiation of cGVHD was demonstrated in a murine allogeneic bone marrow transplantation model in which it was demonstrated that the initial targets for CD8^{+} T-cells in GVHD were restricted to proteins expressed by residual host antigen-presenting dendritic cells [32]. When host dendritic cells were eradicated by conditioning or replaced with donor dendritic cells, thus decreasing the interaction between host antigen-presenting cells and donor CD8^{+} cells, GVHD was attenuated.

Because ECP has been demonstrated to induce an antiidiotype response against leukemia cells in patients with CTCL and autoreactive T-cell clones in scleroderma, we analyzed samples from 9 patients with cGVHD by spectratype analysis for clonal populations of alloreactive T-cells. We detected oligoclonal or monoclonal populations in all 7 patients who demonstrated a clinical response to ECP but not in 2 nonresponders. Although the relevance of these monoclonal T-cell populations in cGVHD patients has not been defined, we speculate that ECP may affect this population of alloreactive cells.

Conclusions

Novel therapies for cGVHD have traditionally targeted activated lymphocyte effectors. ECP may also target host antigen presentation by modulating dendritic cell number and function. Further studies of the immunomodulatory effects of these and other modalities may lead to a better understanding of the mechanisms of cGVHD.

Questions

Participant. Is there a recommended treatment duration for ECP?

Dr. Foss. The treatment discussed was begun at an interval of every other week, continuing to the patient's best clinical response. Subsequently, treatment can then be tapered to once each month, and gradually tapered off thereafter. At the present time we have a number of patients who have responded favorably and have discontinued treatment.

Participant. When can the steroid doses be stopped?

Dr. Foss. We usually begin tapering the immunosuppressive drugs once we see clinical improvement in the patient. Moreover, we have found it advantageous to eliminate drugs such as MMF first and lower the steroids next.

Participant. Concerning the clonality studies presented—did you follow these clonality changes over time?

Dr. Foss. We are currently following 14 patients. We have seen eradication of the clone in several of these patients, but the numbers are not large enough yet to be significant.

Participant. Does the disappearance of the clone persist after the cessation of ECP?

Dr. Foss. We do not yet know this answer. We are presently conducting a comprehensive spectratype analysis on these patients to ascertain what, if any, implications ECP has overall on immune reconstitution.

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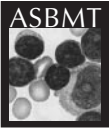
Daniel R. Couriel, MD
Special Situations in the Management of Chronic Graft-versus-Host Disease

The treatment of chronic graft-versus-host disease (cGVHD) remains a complex clinical challenge to physicians. For this presentation I chose 3 particular types of situations that pose a great challenge to successful management and treatment. Specifically, these include: managing the steroid-refractory patient, managing the steroid-refractory patient with cGVHD involving the liver, and managing a variety of technical concerns related to the use of extracorporeal photopheresis (ECP) as an emerging treatment for treatment-refractory cGVHD.

Steroid-Refractory cGVHD

Immunosuppressive therapies combining alternating-day cyclosporine (CsA) with prednisone (PDN) are commonly employed among patients with cGVHD [1,2]. However, the use of such first-line treatment can result in diminishing responses. According to the criteria in place at the MD Anderson Cancer Center (MDACC), patients are deemed steroid-refractory when one of the following situations are met:
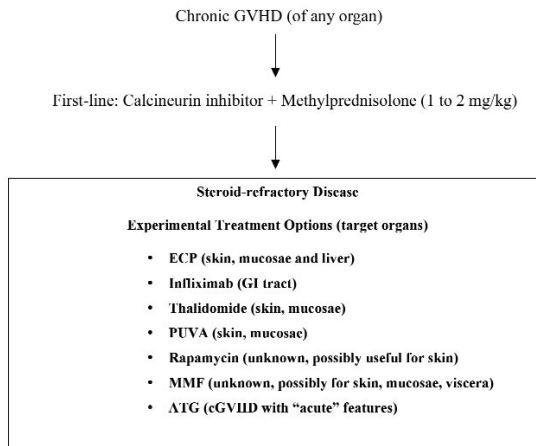
- Stable disease (ie, no response to steroids) is evident for 1 month, or
- Only partial response is evident after 2 months of steroid treatment, or
- Progressive disease despite 1 to 2 weeks on steroid treatment

Once patients become steroid-refractory, a heterogeneous variety of second-line therapies are usually instituted off-protocol, ie, out of the setting of a clinical trial. This variety shows the lack of consistently effective treatments for steroid-refractory cGVHD and the need for new modalities beyond calcineurin inhibitors and steroids. Shown in the Figure is a treatment algorithm that encompasses the management of treatment-refractory cGVHD patients as done at our institution.

Treatment Options
ECP

Although the best choices for treating steroid-refractory cGVHD patients are

Chronic GVHD (of any organ)

↓

First-line: Calcineurin inhibitor + Methylprednisolone (1 to 2 mg/kg)

↓

Steroid-refractory Disease
Experimental Treatment Options (target organs)

- **ECP (skin, mucosae and liver)**
- **Infliximab (GI tract)**
- **Thalidomide (skin, mucosae)**
- **PUVA (skin, mucosae)**
- **Rapamycin (unknown, possibly useful for skin)**
- **MMF (unknown, possibly for skin, mucosae, viscera)**
- **ATG (cGVHD with "acute" features)**

A useful approach to treating cGVHD.

under investigation, encouraging results have been reported with ECP. A 1998 study by Sneicinski et al [3] evaluated the use of ECP with ex vivo injectable psoralen (Uvadex, Therakos, Exton, PA) in 37 patients with hematologic malignancies. Extensive cGVHD was present in all participants despite therapy with first-line CsA, PDN, FK506, thalidomide, or psoralen and UVA (PUVA). Overall, there was a 54% response rate among those treated, with 12 (80%) of 15 patients exhibiting complete or partial resolution of skin hyperpigmentation and extensive scleroderma with ulcerations. Additional improvements in oral ulcerations, gastrointestinal (GI) tract or ocular gland involvement, and pulmonary involvement were observed as well. Across 725 ECP procedures conducted during this study, only 14 adverse events were noted: increased red cell and platelet transfusion needs (n = 7), catheter-related sepsis (n = 4), severe chills (n = 2), and tetanic cramping (n = 1). The investigators concluded that ECP with ex vivo Uvadex yields favorable results for refractory cGVHD of the skin and possibly viscera as well, and could be considered as an early treatment for cGVHD [3].

Infliximab

Separate work by our team at MDACC has resulted in encouraging data with infliximab among patients with cGVHD involving the GI tract [4]. Thirteen

patients with cGVHD and diarrhea who failed treatment with tacrolimus and steroids were given infliximab (10 mg/kg, 4×/week). Ninety-two percent (12 of 13 patients) exhibited complete responses with no acute toxicity and an incidence of infection no greater than usually expected among such patients. Additionally, work from our group further substantiates the successful use of infliximab among cGVHD patients with GI involvement. A separate study of 25 GVHD patients, which included 5 cGVHD patients, revealed complete responses to similar doses of infliximab in 3 cGVHD patients with chronic diarrhea [5]. Based on these collective data, we have added infliximab to our group of off-protocol treatments for chronic GI-related cGVHD.

Thalidomide

We have also included thalidomide among our second-line therapies for skin and oral cGVHD as a result of studies done by Vogelsang and colleagues [6]. This agent has been discussed in detail previously and represents another useful treatment option.

MMF

Mycophenolate mofetil (MMF), an antiproliferative drug that interrupts immune response signaling during DNA synthesis [1], has shown promise in canine model studies of GVHD. Notably, as reviewed by Arai and Vogelsang [1], MMF

Table 1. Approaches to Managing Common Comorbid Conditions among GVHD Patients*

Comorbid Condition	Clinical Recommendation
Anemia	
If Hgb level at or near 9 gm%	Maintain Hgb level ≥ 9 gm%; 10 gm% is preferable
If Hgb level below 9 gm%	Transfuse with RBCs to achieve an Hgb level at or above 9 gm%
	Treatment Goal: maintain Hgb levels around 10 gm%
Thrombocytopenia	
If platelet levels ≥ 100,000/mm^3	Administer heparin
If platelet levels ≤ 100,000/mm^3 or if heparin is contraindicated	Administer ACD-A
	Treatment goal: maintain platelet levels above 20,000/mm^3 while controlling hemostasis

Hgb indicates hemoglobin; RBCs, red blood cells; ACD-A, anticoagulant-citrate-dextrose solution, formula A.

≤2 g/day for adults and 600 mg/m^2 for children, given for a median of 25 days (for aGVHD) or for 94 days (for cGVHD) in addition to continued prophylactic GHVD medications including CsA, PDN, and antithymocyte globulin (ATG)) resulted in complete or partial responses among roughly 33% (4 of 12 patients) of treated patients with chronic steroid-refractory GVHD. Despite MMF doses being reduced in 7 of the 12 (58.3%) cGVHD patients, 7 other cGVHD patients remained alive at the time of the report, with their immunosuppressive drugs being tapered as well [7]. Separate data reported by Basara et al [8] also indicate favorable responses to MMF treatment among cGVHD patients. In this study, patients with acute (n = 17) or chronic (n = 7) GVHD were given MMF in conjunction with CsA and prednisolone. Among the cGVHD patients, moderate improvements were noted in 3 of 6 patients with limited disease. MMF was administered qid as 250-mg oral doses, increasing to a total of 2 g/day after 1 week; dosing was continued unless adverse events occurred. However, MMF was not discontinued in any patients. Hepatic toxicity resulted in 1 patient likely to have multiorgan failure due to progressive disease [8].

Rapamycin (Sirolimus)

Additional treatments exhibiting favorable results include agents such as rapamycin (sirolimus). A macrolide drug with strong immunosuppressive properties (see [9] and references therein), rapamycin is 1 to 2 orders of magnitude more potent than CsA in preventing the rejection of vascularized allografts in animals [9,10]. Moreover, rapamycin possesses minimal renal toxicity as evidenced by rat studies that showed no renal dysfunction upon treatment [9,11].

Rapamycin is structurally similar to tacrolimus, a related immunosuppressive agent [12]. Like tacrolimus, rapamycin also binds to the FK binding protein (FKBP), but unlike tacrolimus, which affects lymphokine production, rapamycin modulates lymphokine responses [12,13]. Importantly, rapamycin exhibits separate and distinct effects on T-cell signal transduction pathways, actually reversing the action of tacrolimus [12]. Although the mechanism of action remains to be clarified, rapamycin, after binding to FKBP, modulates the mammalian target of rapamycin (MTOR) protein, resulting in kinase/cyclin inhibition, blocked IL-2–driven T-cell proliferation and cell cycle arrest in stage G1.

The utility of rapamycin for treatment of GVHD was shown in separate murine studies [9,13]. Blazar and colleagues [13] reported that T-cell expansion as well as the production of Th1 cells and Th1 cytotoxic cytokines were blocked by rapamycin in a murine GVHD model system. Furthermore, these authors also reported that drug treatment inhibited the graft-versus-leukemia (GVL) effect from donor lymphocytes. In another murine-based study by Chen et al [9] rapamycin was found to act synergistically with tacrolimus in extending the survival of a small bowel graft. It is important to note that the synergy reported by Chen et al appears to counter the FKBP binding specificity for both tacrolimus and rapamycin, underscor-

ing that the mechanism remains to be elucidated. However, our clinical experience indicates that combining these agents may be beneficial among GVHD patients.

Recently, we have evaluated the use of rapamycin in a group of 11 very-high-risk cGVHD patients. Of these patients, 8 had extensive cGVHD, 3 had limited disease, and all were resistant to methylprednisone (MP) and tacrolimus. All patients had received 3 to 8 courses of immunosuppressive therapy, and all had been taking MP for more than 30 days prior to the study outset. Ten of these 11 patients exhibited skin GVHD, 5 had visceral involvement, and 6 had mucosal disease. Rapamycin was initiated at a loading dose of 6 mg, followed by maintenance doses of 2 mg/day.

Although complete response to treatment did not occur, 5 patients exhibited partial responses, which were confined to the skin. Overall, rapamycin toxicity was manageable and did not require discontinuation of the drug. Hyperlipidemia (n = 7) was the most common toxicity, followed by thrombocytopenia (n = 1) and leukopenia (n = 1). Five patients expired from their GVHD, yet 3 remain alive at this writing.

Refractory cGVHD of the Liver

ECP has been discussed in earlier sections of this meeting and appears to be a potential treatment for cGVHD. Greinix et al in 1998 showed that in addition to minimal toxicity (predominantly catheter-related infections that resolved posttreatment), ECP resulted in the complete resolution of cutaneous chronic GVHD in 12 of 15 (80%) of those treated. ECP was administered on 2 consecutive days at 2-week intervals for 3 months, then every 4 weeks until resolution. Moreover, oral GVHD resolved in 100% of treated patients, and liver GVHD in 70% as well [14].

As noted, ECP has led to encouraging outcomes among cGVHD patients with oral and dermal disease. At MD Anderson, we are now extending the application of ECP to steroid-refractory cGVHD of the liver. Eighteen steroid-refractory patients, 11 with cGVHD and 7 with aGVHD of the liver, were treated with an intensive ECP regimen. As such, ECP was administered
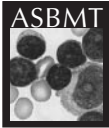
Table 2. Anticoagulation Ratios Adjusted to Platelet Count in ECP

ACD-A:Blood Ratio*	Threshold Platelet Level†
1:8	>500,000
1:10	100,000 to 499,000
1:12	50,000 to 99,000
1:14	20,000 to 49,000

*Defined as 1 volume unit of ACD-A to x volume units of peripheral blood. ACD-A indicates anticoagulant-citrate-dextrose solution, formula A.
†Data are expressed as cells per mm³.

3×/week until responses were obtained and then tapered to 2 treatments every 2 weeks. We observed the majority of responses in approximately 2 to 3 months.

Among the 11 evaluable patients, 6 (54.5%) responded to treatment, with 2 complete responders among cGVHD patients and 4 partial responders, 1 of whom had aGVHD. An additional 2 patients were nonresponders, and the remaining 3 patients had progressive GVHD. Seven of 18 patients were not evaluable because of early death.

ECP can induce responses in about 50% of patients with acute and chronic GVHD involving the liver, a organ known to not respond favorably to immunosuppression. ECP may be an effective therapy early in the course of liver GVHD.

Comorbid Clinical Considerations Surrounding ECP in Treating cGVHD

The findings surrounding ECP and its use in treating GVHD are encouraging; however, one must not lose sight of the fact that patients with cGVHD are often high-risk cases with suboptimal prognoses. ECP, it appears, may be able to alter the prognosis, but not without individualized, multidisciplinary approaches to patient care.

Despite specific organ involvement, GVHD is a systemic disease. To ensure that ECP treatments yield their most favorable responses, we at MD Anderson have instituted additional guidelines for managing our GVHD patients with complicating comorbid conditions such as anemia and thrombocytopenia. As shown in the Table 1, these hematologic abnormalities can be successfully managed provided target hemoglobin ((9 gm%) and platelet levels (>20,000) are maintained. Importantly, because thrombocytopenic patients possess coagulation abnormalities as well, we have instituted a series of proportions governing the ratio of anticoagulation levels to platelet levels. Table 2 illustrates the ratios we have found to be acceptable, thereby aiding in managing hemostasis as well. By adhering to these guidelines, we have had excellent tolerance for ECP alongside such complicating factors.

Conclusions

Successful treatment of cGVHD patients has come to rely on a variety of treatments, both old and new. The treatment of cGVHD must incorporate, in addition to different immunosuppressive modalities, a multidisciplinary approach so as to more thoroughly manage the complications of the disease and improve quality of life. Finally, new therapies such as ECP are showing encouraging results. It is hoped that these emerging treatments will further improve the outcomes of GVHD patients. Ongoing clinical trials will confirm the data reported thus far, hopefully resulting in longer survival times and more robust responses becoming the rule rather than the exception.

Questions

Participant. What is your rationale for selecting the number of ECP cycles to be used in a particular protocol?

Dr. Couriel. There is no rationale. Unfortunately dose-finding studies are not the rule in the treatment of GVHD. The same counts for ECP. As this technique is more rigorously studied, we will be able to compare different schedules and make appropriate adjustments to them.

Participant. Because your frequency of ECP administration is greater than that cited in previous reports, do you have a greater incidence of infections?

Dr. Couriel. Aside from occasional catheter-related infections, we do not have a greater incidence of infections.

Participant. Are discordant responses to ECP observed between different organs?

Dr. Couriel. Yes, definitely. For example, you may see skin respond and the GI tract get worse at the same time.

Participant. What type of catheter are you using for ECP?

Dr. Couriel. We use a Quinton catheter.

Participant. Can you comment on how platelet levels can change during ECP?

Dr. Couriel. Yes, you may see transient thrombocytopenias. These are completely reversed when you decrease the frequency of treatment.

Participant. What is the overall efficacy of the therapies you have described for cGVHD?

Dr. Couriel. It varies with the treatment. For example, ECP for cGVHD of the skin, mucosae, and liver seems to be responsive and worth investigation. Rapamycin can achieve responses in cGVHD of the skin. In our study, rapamycin is used in combination with tacrolimus.

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JOURNAL Watch

A scan of recent medical literature identi-fied these articles of special importance in the science and clinical application of blood and marrow transplantation.

Ciancio G, Miller J, Garcia-Morales R, et al: Six-year clinical effect of donor bone marrow infusions in renal transplant patients. Transplantation 71:827-835, 2001.

The long-term results of donor bone marrow cell (DBMC) infusions in renal transplant recipients were evaluated. The study included 63 cadaver renal transplant recipients who were given one or two DBMC infusions. Each donor-recipient pair had at least one HLA-DR antigen mismatch. One group of 42 patients received a mean DBMC dosage of 7.01×10^8/kg, infused on postoperative days 4 and 11; the remaining 21 patients received one half of that dose on day 4. Two hundred nineteen patients who did not receive DBMC infusion were studied for comparison. The immunosuppressive regimen consisted of a 10-day course of OKT3 induction, with tacrolimus, mycophenolate mofetil, and methylprednisolone mainte-nance. Outcomes were compared at a mean follow-up of 4.7 years.

Aside from the use of DBMC infusions, the two groups were comparable in terms of immunosuppressive therapy and demo-graphic characteristics. The rate of biopsy-confirmed chronic rejection was just 3% in the DBMC group, compared with 18% in the comparison group. Actuarial 6.3-year graft survival rates were comparable: 84.3% in the DBMC group and 72.2% in the control group. However, the difference was significant on exclusion of patients who died with a functioning graft: 94.1% in the DBMC group versus 79.8% in the control group.

Only 2 of the DBMC recipients had ongoing deterioration in kidney function, compared with 40 in the comparison group. Serial iliac crest bone marrow spec-imens showed a tripling of chimerism in the DBMC group from years 1 to 4. There was no evidence of developing chimerism in the comparison group.

This study provides evidence of the long-term effectiveness of DBMC infu-sions to induce specific immunologic unre-sponsiveness in renal transplant recipients. Compared to noninfused patients receiving equivalent immunosuppression, patients receiving DBMCs have better long-term graft survival with increasing bone marrow chimerism. The authors are performing careful studies of immunosuppressive with-drawal in this patient population.

Johnson BD, Dagher N, Stankowski MC, et al: Donor natural killer (NK1.1⁺) cells do not play a role in the suppres-sion of GVHD or in the mediation of GVL reactions after DLI. Biol Blood Marrow Transplant 7:589-595, 2001.

In patients undergoing allogeneic BMT for relapsed disease, delayed donor leuko-cyte infusions (DLI) have a potent graft-versus-leukemia (GVL) effect. This GVL effect may involve both T cells and natural killer cells; mouse models support a role for donor regulatory T cells. However, the con-tribution of NK T cells to suppression of graft-versus-host (GVH) reactivity and induction of the GVL effect remain uncer-tain. The impact of donor NK cell depletion on the effects of DLI were studied in the murine C57BL/6 into AKR model of BMT.

Recipient animals were treated with an anti-NK1.1 monoclonal antibody—clone PK136—for in vivo depletion of donor NK cells. The NK-depleted and non–NK-depleted chimeras were compared for their effects on suppression of GVH reac-tivity and on mediation of the GVL response after DLI.

The number of splenic NK1.1⁺ cells was significantly reduced in anti-NK1.1–treated chimeras. Splenocytes from mice receiving the anti-NK1.1 antibody demonstrated a significant reduction in lymphokine-activated lytic activity. However, NK deple-tion did not significantly alter the level of GVH reactivity after DLI. Furthermore, there was no difference in GVL reactivity in response to acute T cell leukemia chal-lenge in DLI-treated chimeras.

In this mouse model of BMT, NK cells appear to play little role in the effects of DLI in suppressing the GVH response or in inducing GVL reactivity. The authors plan further studies to identify other cell surface markers—eg, CD25—capable of identifying the T cells responsible for the GVH-suppressing effect of DLI.

Kook H, Zeng W, Guibin C, et al: Increased cytotoxic T cells with effec-tor phenotype in aplastic anemia and myelodysplasia. Exp Hematol 29:1270-1277, 2001.

The development of autoimmunity in patients with aplastic anemia (AA) may reflect the expansion of cytotoxic lympho-cytes (CTLs) with a mature effector phe-notype. This hypothesis was tested by com-paring effector CTL numbers in patients with AA and other bone marrow failure syndromes.

The study included 91 patients with AA, before or after immunosuppressive therapy; 12 patients with myelodysplastic syndrome (MDS); 7 patients with other, nonimmune hematologic diseases; and 16 normal controls. Four-color flow cytometry was performed to examine the presence of effector T lymphocytes. The terminal effector phenotype was assessed in terms of CD57 expression and loss of CD28 on CD8⁺CD3⁺ CTLs.

Patients with AA or MDS had higher percentages of CD8⁺CD28⁻ cells than those in hematologic or normal control groups. The effector CTL population tended to be highest in previously untreated patients and those with no response to immunosuppres-sive therapy, intermediate in partial and complete responders, and lowest in controls. The degree of pancytopenia was unrelated to the size of the effector cell population.

Intracellular staining for perforin and granzyme B in CTLs showed no differ-ences between AA patients and controls.

Patients with AA or MDS have an increased effector CTL population com-pared to controls or multiply transfused patients with nonimmune hematologic dis-eases. Measurements of the effector cell population provide little insight into the pathophysiology of AA. However, the effector CTL phenotype may be useful in

studying antigen-specific T cells in this disease, and thus in identifying potential causative agents.

Keever-Taylor CA, Bredeson C, Loberiza FR, et al: Analysis of risk factors for the development of GVHD after T cell–depleted allogeneic BMT: effect of HLA disparity, ABO incompatibility, and method of T-cell depletion. Biol Blood Marrow Transplant 7:620-630, 2001.

Partial T-cell depletion (TCD) of marrow allografts can reduce the risk of acute graft-versus-host disease (GVHD), and extensive TCD also may reduce the incidence of chronic GVHD. However, most studies have shown no significant impact on survival. The authors reviewed their 9-year experience with TCD marrow allografting to identify factors influencing the risk of acute and chronic GVHD—including the TCD method used.

The analysis included 481 patients undergoing TCD marrow allografting from 1991 to 2000. In 400 patients, partial depletion of $CD3^+$ T cells was achieved by complement-mediated lysis using the narrow-specificity monoclonal antibody T10B9.1A-31. For the remaining 81 patients, TCD was performed using Muromonab-Orthoclone OKT3. Multivariate analysis was performed to evaluate a wide range of factors potentially affecting the risk of grade II to IV acute GVHD and extensive chronic GVHD.

Compared to patients with baseline matched siblings, the relative risk (RR) of acute GVHD was 2.09 for recipients of related donor grafts with 2 or more mismatched HLA antigens, 1.98 for recipients of matched unrelated donor grafts, and 2.68 for recipients of unrelated donor grafts with 2 or more HLA mismatches. Acute GVHD risk was not increased for recipients of family marrow with 0 to 1 mismatches, nor for those with 1 antigen mismatched unrelated donors. Minor ABO disparity doubled the risk of acute GVHD, but major or major-minor ABO disparity had no effect.

For the OKT3 group, TCD was less effective, leading to a higher T cell dose.

The use of OKT3 was associated with a higher risk of acute GVHD (RR 1.84) but with the OKT3 cohort, the T cell dose was not.

Risk of extensive chronic GVHD was higher for patients older than 20 years (RR 2.2); and for cytomegalovirus (CMV)-positive recipients with CMV-negative donors (RR 1.9). Risk factors for reduced survival were older than 20 years, related donor with 2 or more HLA mismatches, unrelated donor with 1 or more HLA mismatches, diagnosis risk group, and CMV-positive recipient/CMV-negative donor.

The authors conclude that the results of TCD marrow allografting are significantly affected by the TCD technique used and suggest that the findings have important implications for donor selection: for example, a CMV-positive donor may be the best choice for a CMV-positive recipient, and minor ABO mismatches should be avoided. Advances in HLA typing will help to identify appropriate donors with 1 or fewer HLA disparities, while avoiding those with 2 or more disparities.