Biology of Blood and Marrow Transplantation 8:387-394 (2002)

Response of 443 Patients to Steroids as Primary Therapy for Acute Graft-versus-Host Disease: Comparison of Grading Systems

Margaret L. MacMillan,[1,4] Daniel J. Weisdorf,[2,4] John E. Wagner,[1,4] Todd E. DeFor,[3,4] Linda J. Burns,[2,4] Norma K.C. Ramsay,[1,4] Stella M. Davies,[1,4] Bruce R. Blazar[1,4]

Departments of [1]Pediatrics, [2]Medicine, [3]Biostatistics, and the [4]Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, Minnesota

Correspondence and reprint requests: Dr. M. L. MacMillan, MMC 484, University of Minnesota, 420 Delaware St SE, Minneapolis, MN 55455 (e-mail: macmi002@tc.umn.edu).

Received March 25, 2002; accepted May 10, 2002

ABSTRACT

Acute GVHD remains a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). In a retrospective analysis, the response of 443 HSCT patients who received prednisone, 60 mg/m^2, for 14 days followed by an 8-week taper, as initial therapy for acute GVHD from 1990 through 1999 at a single institution was examined. Median patient age was 29.0 years (range, 0.3-60.3 years), with 40% of patients <20 years old. Patients received HSCT from 201 related (189 matched sibling/ 12 partially matched) and 242 unrelated (130 HLA-A, B, DRB1 matched/112 partially matched) donors. GVHD score was measured and outcomes compared using the Minnesota, Consensus, and International Bone Marrow Transplant Registry (IBMTR) grading systems. Prior to initiation of steroid therapy, severe (grades III-IV) acute GVHD was observed in 57 (13%) patients (Minnesota or Consensus grading) and in 192 (43%) patients (IBMTR grading). At day 28 of treatment, overall improvement was observed in 55% of patients, with durable (≥28 days) complete response observed in 35% and partial response observed in 20% of patients. Patients with acute lower gastrointestinal GVHD (± other organ involvement) had lower response rates. In multivariate logistic regression analysis, recipients of related donor grafts and recipients of GVHD prophylaxis other than methotrexate alone had the highest likelihood of overall response. Initial Minnesota GVHD grade or Consensus GVHD grade was not associated with significant differences in overall response, whereas patients with an initial IBMTR grade of B or C had a higher likelihood of response. Chronic GVHD developed in 42% of patients by 1 year after HSCT. The probability of survival at 1 year after initiation of steroid therapy was 53% (95% confidence interval, 48%-58%). In Cox regression analysis, factors associated with better survival included patients' youth, receipt of related or HLA-matched unrelated grafts, and administration of GVHD prophylaxis other than T-cell depletion in all 3 grading systems. Lower initial GVHD grade (I-II or A-B) led to better survival. These data suggest that steroids provide an active but inadequate therapy for acute GVHD, especially with highergrade GVHD. More effective prophylaxis and therapy for acute GVHD is needed for mismatched unrelated donor recipients and for those with severe GVHD.

KEY WORDS

Acute GVHD • Steroids • Primary therapy • Hematopoietic stem cell transplantation • GVHD grading systems

INTRODUCTION

Acute graft-versus-host disease (GVHD) is a significant cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). The effectiveness of steroids as front-line therapy was primarily assessed in the 1980s, and response rates of about 50% were reported [1-6]. However, since then, the nature of HSC donors has dramatically changed with the frequent use of unrelated donor (URD) HSC. In addition, different GVHD grading systems have been developed with varying abilities to predict outcomes after GVHD therapy.

To assess the impact of systemic steroids as initial therapy for acute GVHD in the past decade, we retrospectively analyzed the clinical response and survival of 443 HSCT

Table 1. *Clinical Features of Patients with Acute GVHD (N = 443)*

Features	No. of Patients (%)
Age	
<20 y	175 (40)
20-39 y	152 (34)
≥40 y	116 (26)
Median (range), y	29 (0.3-60)
Year of Transplantation	
1990-1992	82 (18)
1993-1995	181 (41)
1996-1999	180 (41)
Male:Female Ratio	266:177 (3:2)
Male recipient/male donor	157 (35)
Male recipient/female donor	107 (24)
Female recipient/male donor	80 (18)
Female recipient/female donor	97 (22)
Male recipient/unknown donor	2 (1)
Diagnosis	
Acute lymphoblastic leukemia	75 (17)
Acute myelogenous leukemia	91 (20)
Chronic myelogenous leukemia	139 (31)
Myelodysplastic syndrome	36 (8)
Other leukemias	4 (1)
Other malignancy	17 (4)
Metabolic disorder	34 (8)
Aplastic anemia/bone marrow failure	26 (6)
Immunodeficiency	21 (5)
Donor type	
Matched related	189 (43)
Mismatched related	12 (3)
Matched unrelated	130 (29)
Mismatched unrelated	112 (25)
Preparative therapy	
Cyclophosphamide and TBI	338 (76)
Other chemotherapy and TBI	54 (12)
Chemotherapy alone	51 (12)
GVHD prophylaxis	
CSA containing	329 (74)
MTX containing (no CSA)	29 (7)
T-cell depletion	70 (16)
Tacrolimus	15 (3)

patients, uniformly treated at a single institution from 1990 through 1999 on a protocol of prednisone, 60 mg/m^2 (or methylprednisolone equivalent) for 14 days followed by an 8-week taper. Response to therapy was analyzed by taking into account 3 different acute GVHD grading methods, the Minnesota [3,7], Consensus [7], and International Bone Marrow Transplant Registry (IBMTR) [8] grading systems.

PATIENTS AND METHODS

Patients

Clinical and laboratory data were retrieved from the University of Minnesota Blood and Marrow Transplant (BMT) Database, which systematically and prospectively collects data on all consecutive patients undergoing transplantation at our institution. Patients were eligible for the study if they developed within 120 days after HSCT grades II to IV acute GVHD as defined by the Minnesota criteria. Patients with limited (grade I) skin acute GVHD were eligible if there was progression of disease within 7 days or no improvement after 10 days of topical steroid therapy. From January 1990 to December 1999, 1181 patients received an allogeneic HSCT at the University of Minnesota. All transplantation and GVHD protocols were reviewed and approved by the Institutional Review Board. All patients and/or guardians gave informed consent. Of these 1181 patients, 741 (63%) developed acute GVHD, of which 443 (60%) received systemic steroid therapy as initial therapy and were enrolled in this study.

Patient characteristics, including underlying disease, type of donor, and GVHD prophylaxis, are shown in Table 1. Patients received their HSCT from January 1990 to December 1999 and were followed for a median of 3.9 years (range, 1.0-9.4 years). HSC sources included bone marrow (BM, n = 378), peripheral blood stem cells (PBSC, n = 39), and umbilical cord blood (UCB, n = 26). Details of the preparative therapy and GVHD prophylaxis, as well as supportive therapy techniques, have been previously reported [9-16]. Eighty-eight percent of patients received a total body irradiation (TBI)-based regimen, and 12% of patients received a chemotherapy-alone regimen. GVHD prophylaxis consisted of cyclosporin A (CSA)-based therapy in 74% of patients, T-cell depletion in 16% of patients, methotrexate (MTX) alone in 7% of patients, and tacrolimus-based therapy in 3% of patients.

Diagnosis, Staging, and Grading of GVHD

Acute GVHD was diagnosed clinically with histological confirmation whenever possible. Symptoms of acute GVHD were graded by 3 separate grading systems, Minnesota, Consensus, and IBMTR (Table 2). The Minnesota system was derived from standard clinical criteria modified to include upper gastrointestinal (GI) acute GVHD [3,7]. The Consensus grading system [7] and the IBMTR severity index [8] were also used. The Minnesota and Consensus systems are similar except for the liver and lower GI staging criteria for grades III and IV GVHD. The IBMTR index is the most different and tends to give a higher GVHD score for a given combination of GVHD stages.

Table 2. *Acute GVHD Grading Systems*

Grade*	Skin†	Liver	GI	Upper GI
Minnesota [3,7]				
I	1-2	0	0	0
II	3	1	1	1
III	—	2-4	2-3	
IV	4	—	4	
Consensus [7]				
I	1-2	0	0	0
II	3	1	1	1
III	—	2-3	2-4	
IV	4	4	—	
IBMTR [8]‡				
A	1	0	0	0
B	2	1-2	1-2	1
C	3	3	3	
D	4	4	4	

*Each grade is based on maximum stage for each involved organ.
†Each column identifies minimum stage for organ grade.
‡Modified as shown to include upper GI GVHD.

Grade of GVHD refers to clinical (not histologic) grade throughout this report. Initial score was calculated using the maximum stage in each organ within a 10-day window (–5 to +5 days) of initiation of steroid therapy. Real-time staging of each organ was determined by the attending physician, supported by laboratory and clinical information abstracted from the medical records. The overall grade was determined by a computer algorithm incorporating all available clinical GVHD organ staging data, centrally reviewed by the GVHD Grading Committee at our center (S.M.D., D.J.W.) and prospectively recorded in the University of Minnesota BMT Database. To make the IBMTR grading comparable to Minnesota and the Consensus grading, we assigned an IBMTR B index value to patients who had initial upper GI acute GVHD with a IBMTR score of grade B or lower.

GVHD Therapy

All patients received a daily thrice-divided dose of prednisone 60 mg/m^2 by mouth (PO) (or methylprednisolone intravenous equivalent, 48 mg/m^2) for 7 consecutive days, then a daily single dose of prednisone for 7 days as initial therapy for acute GVHD. Patients were maintained on therapeutic levels of CSA in 329 patients (74%) or tacrolimus in 15 patients (3%). Additionally, patients with acute skin GVHD were treated with topical 0.1% triamcinolone cream or 1% hydrocortisone cream (for facial rash) 3 times daily. If a complete response to prednisone was observed, patients continued therapy with single-dose prednisone 60 mg/m^2 per day PO for a total of 14 days and then commenced a taper of steroids over 8 weeks [17].

Patients received supportive care that included ongoing prophylaxis for bacterial infections (250 mg penicillin VK [penicillin V potassium] PO, twice a day) and fungal infections (clotrimazole, nystatin, or fluconazole), *pneumocystis carinii* pneumonia (trimethoprim-sulfa double strength twice daily every Monday and Tuesday), and cytomegalovirus (CMV) (800 mg acyclovir PO 5 times per day). Children received the same prophylaxis appropriately dose-adjusted for weight.

Measurement of GVHD Response to Prednisone

Response to therapy was evaluated by the attending physician and prospectively recorded in the University of Minnesota BMT Database at treatment days 7, 14, 21, 28, and 42 by determining the GVHD clinical stage score for each time point (±3 days) [5]. The day 28 response was determined from the maximum acute GVHD grade in each organ observed 28 days (±14 days) after prednisone treatment was initiated. Complete response (CR) was defined as the complete resolution of all acute GVHD symptomatology in all organs. This score had to be maintained for 28 days (ie, beyond day 56 after initiating prednisone therapy) without additional treatment to be considered a CR. Partial response (PR) was defined as durable (≥28 further days) improvement in GVHD stage in all initial GVHD target organs without complete resolution and without worsening in any other GVHD target organs. No response (NR) was defined as the same grade of GVHD or progression of GVHD in any organ or death before day 28 after prednisone initiation. Progression was defined as worsening GVHD in ≥1 organ with or without amelioration in any organ. Steroid-resistant acute GVHD was defined as progression of acute GVHD after 4 days of treatment with prednisone or no improvement of acute GVHD after 7 days of treatment with prednisone. Patients with steroid-resistant GVHD were treated with secondary therapy.

For assessment of treatment response, a GVHD organ stage score was determined for each patient, as previously described [2]. This stage score represented the sum of each acute GVHD organ stage (0-4) plus 1 point for upper GI involvement and thus had a maximum possible score of 13.

Statistical Analysis

The major endpoints of this study were response to GVHD therapy at day 28 after treatment and survival. Univariate analysis of response to therapy was performed by Pearson's chi-square test. The independent effect of study variables on response was determined using logistic regression [18].

Survival was measured from the time of initiation of therapy with prednisone. The Kaplan-Meier method was used to estimate survival with 95% confidence intervals derived from standard errors [19]. Comparison within study cohorts was completed by the log-rank statistic. Cox regression was used to determine the independent effect of these factors [20]. Cumulative incidence curves were calculated to estimate the incidence of chronic GVHD and infectious complications. Deaths from other causes were treated as competing risks [21].

Study variables considered included age, year of transplantation, sex, sex match, diagnosis, type of donor (related, matched unrelated, mismatched unrelated), CMV serostatus of the patient and donor, GVHD prophylaxis regimen, conditioning regimen, initial grade of acute GVHD, time to onset of acute GVHD, time to therapy, and type of organ involvement. The effect of response to therapy on survival was also investigated as a time-dependent covariate.

RESULTS

Maximum initial GVHD stage in each organ for each patient is shown in Table 3. The GVHD grade at time of initiation of steroid therapy is shown in Table 4. With both the Minnesota and Consensus grading systems, the initial GVHD grades were grade I in 122 patients (28%), grade II in 264 patients (60%), grade III in 50 patients (11%), and grade IV in 7 patients (2%). With the IBMTR severity index, the initial GVHD grades were grade A in 83 patients (19%), grade B in 168 patients (38%), grade C in 181 patients (41%), and grade D in 11 patients (2%). Median time to onset of GVHD from day of HSCT was 27 days (range,

Table 3. *Maximum Initial GVHD Stage at the Onset of Prednisone Therapy**

	0	1	2	3	4
Skin	87 (20%)	48 (11%)	136 (31%)	169 (37%)	3 (1%)
Liver	415 (94%)	9 (2%)	7 (1%)	8 (2%)	4 (1%)
Rectal	362 (82%)	46 (10%)	18 (4%)	13 (3%)	4 (1%)
Upper GI	335 (76%)	108 (24%)			

*Maximum stage during window (–5 to +5 days) around initiation of prednisone therapy.

Table 4. *Initial Acute GVHD Grade*

Grading System	Grade I or A	Grade II or B	Grade III or C	Grade IV or D
Minnesota	122 (28%)	264 (60%)	50 (11%)	7 (2%)
Consensus	122 (28%)	264 (60%)	50 (11%)	7 (2%)
IBMTR	31 (7%)	220 (50%)	181 (41%)	11 (2%)

8-94 days). Median time to treatment with prednisone from day of HSCT was 30 days (range, 8-94 days).

Of the 443 patients treated with prednisone, durable response (CR + PR) was observed in 245 patients (55%) by day 28 after initiation of therapy. CR was achieved in 157 patients (35%), PR in 88 patients (20%), and NR in 178 patients (40%). Twenty patients (5%) were unevaluable because of early death but were considered as treatment failures for the purpose of analysis.

Various patient characteristics and transplantation conditions were analyzed for their association with clinical response to prednisone therapy by day 28. In univariate analysis, factors associated with a statistically significant higher likelihood of CR/PR included year of HSCT, type of HSC donor, GVHD prophylaxis, and initial GVHD IBMTR grade. CR/PR was achieved in 35 (43%) of 82 patients who received transplants in 1990-1992, 101 (56%) of 181 patients who received transplants in 1993-1995, and 109 (61%) of 180 patients who received transplants in 1996-1999 ($P = .03$). CR/PR was observed in 118 (59%) of 201 related donor recipients compared to that in 76 (58%) of 130 HLA-matched URD recipients and 51 (46%) of 112 mismatched URD recipients ($P = .05$). Only 9 (31%) of 29 patients given MTX alone as GVHD prophylaxis achieved a response to steroids compared to 188 (57%) of 329 patients given CSA-containing GVHD prophylaxis, 38 (54%) of 70 recipients of T-cell–depleted grafts, and 10 (67%) of 15 patients given tacrolimus ($P = .04$). There was no association between CR/PR following steroid treatment and patient age, sex, diagnosis, CMV serostatus, preparative therapy, time to onset of GVHD, or time from diagnosis of GVHD to initiation of systemic steroid therapy.

The response to steroid treatment among patients with various combinations of organ involvement was analyzed. The number of organs involved with acute GVHD was not a prognostic indicator of response, as response was observed in 91 (54%) of 170 patients with 1 organ involved with GVHD, 82 (52%) of 157 patients with 2 organs involved, and 72 (62%) of 116 patients with 3 or 4 organs involved ($P = .23$). Patients with lower GI acute GHVD (± other organ involvement) responded less often. Of the 81 patients with lower GI involvement, 34 (42%) achieved CR/PR versus 211 (58%) of 362 patients without lower GI involvement ($P < .01$). The only statistically significant combination of organ involvement was that of lower GI and skin GVHD. Twenty-one (42%) of 50 patients with lower GI and skin acute GVHD obtained CR/PR versus 224 (57%) of 393 patients without this combination ($P = .04$). Organ stage score was not predictive of response to GVHD treatment.

The clinical factors relevant to the likelihood of achieving CR/PR were examined in a logistic regression analysis using each GVHD grading system (Table 5). In each grading system, HLA-mismatched URD recipients were less likely to respond to steroid therapy than were related donor recipients or HLA-matched URD recipients. Additionally, using each grading system, the use of MTX for GVHD prophylaxis was associated with a lower probability of response to steroids. There was a tendency toward lower response to steroids with higher initial GVHD grade as scored by the Minnesota and Consensus methods, although this was not statistically significant (Figure 1). Surprisingly, using the IBMTR index, patients with initial grade B or C GVHD had a higher probability of responding to steroid therapy than did patients with initial grade A GVHD. Patients with

Table 5. *Factors Associated with CR/PR in Acute GVHD: Logistic Regression Analysis*

Grading System and Variable	Relative Likelihood of CR/PR (95% CI)	*P*
Minnesota		
Type of donor		
Related	1.0	
Matched unrelated	0.8 (0.5-1.4)	.52
Mismatched unrelated	0.5 (0.3-0.8)	<.01
GVHD prophylaxis		
CSA	1.0	
MTX	0.3 (0.1-0.6)	<.01
T-cell depletion	0.9 (0.5-1.6)	.77
Tacrolimus	1.2 (0.4-3.8)	.63
Initial grade of GVHD		
I	1.0	
II	0.9 (0.6-1.5)	.79
III	0.8 (0.4-1.7)	.66
IV	0.3 (0.1-1.9)	.23
Consensus		
Type of donor		
Related	1.0	
Matched unrelated	0.8 (0.5-1.4)	.47
Mismatched unrelated	0.5 (0.3-0.8)	<.01
GVHD prophylaxis		
CSA	1.0	
MTX	0.3 (0.1-0.6)	<.01
T-cell depletion	0.9 (0.5-1.6)	.78
Tacrolimus	1.2 (0.4-3.8)	.71
Initial grade of GVHD		
I	1.0	
II	0.9 (0.6-1.5)	.78
III	0.8 (0.4-1.5)	.47
IV	0.7 (0.2-3.5)	.66
IBMTR		
Type of donor		
Related	1.0	
Matched unrelated	1.0 (0.6-1.6)	>.80
Mismatched unrelated	0.6 (0.3-1.0)	.04
GVHD prophylaxis		
CSA	1.0	
MTX	0.2 (0.1-0.6)	<.01
T-cell depletion	0.8 (0.5-1.4)	.59
Tacrolimus	0.9 (0.3-2.9)	>.80
Initial grade of GVHD		
A	1.0	
B	2.5 (1.2-5.3)	.01
C	1.7 (0.8-3.6)	.15
D	0.7 (0.1-3.1)	.62

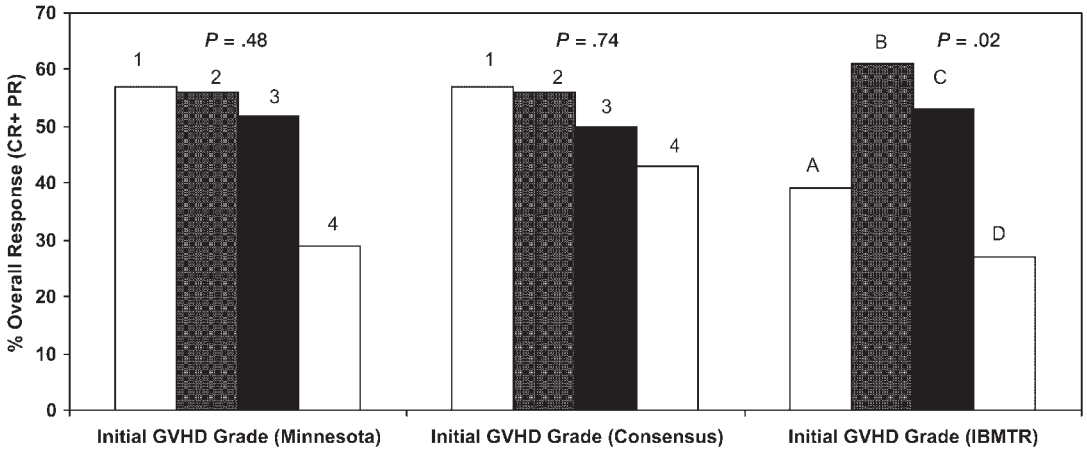

Figure 1. Initial acute GVHD grade and overall response to steroid therapy.

IBMTR grade A GVHD (rash involving less than 25% of body surface) had a lower probability of CR or PR than did those with IBMTR grade B or C GVHD. The 31 patients with initial IBMTR grade A GHVD were similar in age and distribution of diagnoses to those with grade B or C (data not shown). Additionally, the median number of days from the time of GVHD diagnosis to initiation of steroid therapy was similar (2 days for grade A patients [n = 31], 1 day for grade B patients [n = 220], 1 day for grade C patients [n = 181], and 4 days for grade D patients [n = 11]). Patients with grade A GVHD had to attain complete resolution of their stage I skin rash to achieve a PR or CR. Any residual rash would constitute treatment failure. Age and year of HSCT were not significant predictors of response to steroids in the multiple regression analyses.

Chronic GVHD

One year after initiation of steroid therapy, 187 patients had developed chronic GVHD, resulting in a cumulative incidence of 42% (95% confidence interval [CI], 37%-47%). With the Minnesota grading system, chronic GVHD developed in 48 (39%) of the 122 patients (95% CI, 30%-48%) with initial grade I GVHD, 117 (44%) of the 264 patients (95% CI, 37%-51%) with initial grade II GVHD, 21 (42%) of 50 patients with initial grade III GVHD (95% CI, 27%-57%), and 1 (14%) of 7 patients with grade IV GVHD (95% CI, 0%-34%; $P = .39$). In contrast, with the IBMTR grading system, chronic GVHD developed in 15 (48%) of the 31 patients (95% CI, 28%-68%) with initial grade A GVHD, 93 (42%) of the 220 patients (95% CI, 35%-49%) with initial grade B GVHD, 76 (42%) of 181 patients with initial grade C GVHD (95% CI, 34%-50%), and 3 (27%) of 11 patients with grade D GVHD (95% CI, 3%-51%; $P = .76$). Sixty-four (41%) of 157 patients who had CR to steroids later developed chronic GVHD (95% CI, 33%-49%), 42 (48%) of 88 who had PR later developed chronic GVHD (95% CI, 36%-60%), and 81 (46%) of 178 who had NR later developed chronic GVHD (95% CI, 38%-54%; $P < .01$).

Infectious Complications

Within the first 100 days after initiation of steroid therapy for GVHD, 182 patients (41%) developed bacterial infections (95% CI, 37%-45%), 14 patients (3%) developed fungal infections (95% CI, 1%-5%), and 96 patients (22%) developed CMV antigenemia (95% CI, 18%-26%). Only 1 patient developed posttransplantation lymphoproliferative disease by day 100 after steroid therapy.

Survival

In the entire cohort of 443 patients, 234 were alive 1 year after initiation of treatment, with a Kaplan-Meier estimate of 53% (95% CI, 48%-58%) survival at 1 year. Various clinical factors were examined for their association with improved survival. The probability of survival 12 months after administration of steroids was 58% (95% CI, 52%-64%) in related donor recipients, 53% (95% CI, 45%-61%) in HLA-matched URD recipients, and 44% (95% CI, 34%-52%) in HLA-mismatched URD recipients ($P = .05$) (Figure 2). Recipients of T-cell–replete grafts had a higher probability of survival at 1 year than did recipients of T-cell–depleted grafts (55% [95% CI, 50%-60%] versus 40% [95% CI, 29%-51%]; $P = .01$). With each GVHD grading system, a lower initial GVHD grade was associated with a higher probability of survival (Figure 3). In addition, a higher organ stage score was associated with a lower probability of 1-year survival ($P < .01$). Other clinical factors,

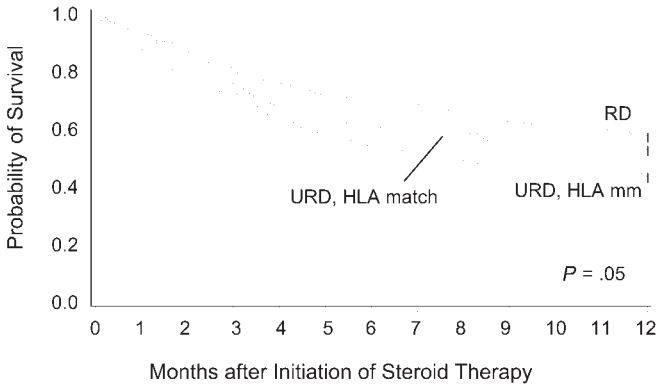

Figure 2. The effect of HSC donor type on survival 1 year after initiation of steroid therapy.

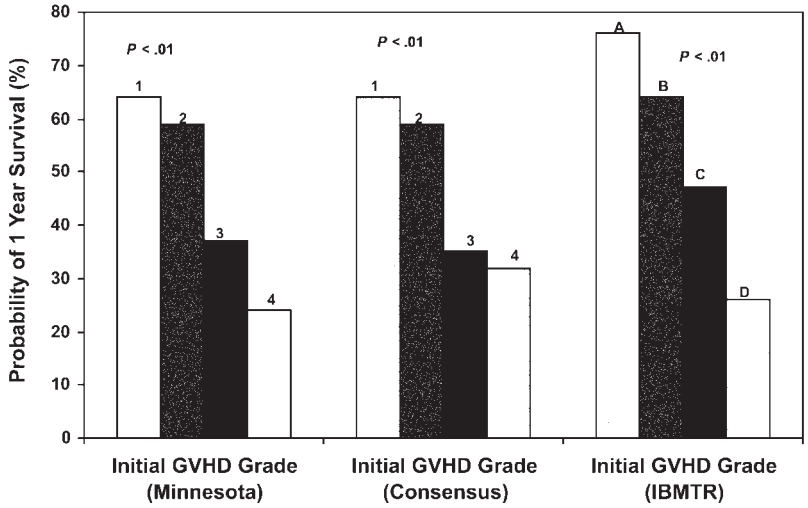

Figure 3. Initial acute GVHD grade and probability of survival 1 year after initiation of steroid therapy.

including age and sex of recipient, year of transplantation, underlying diagnosis, preparative therapy, source of stem cells (BM versus UCB versus PBSC), and CMV serostatus, had no association with survival.

In Cox regression analysis, the use of a related donor or HLA-matched unrelated graft, CSA as GVHD prophylaxis, younger age at time of HSCT, and lower grade of initial GVHD grade using each grading method were independently associated with greater survival (Table 6).

Causes of Death

Fifty-four patients died within 1 year after initiation of steroid therapy. The primary cause of death was GVHD in 48 patients (89%) and relapse in 6 patients (11%). Infections were a contributing cause of death in 36 deaths (67%).

DISCUSSION

This study represents the largest series from a single institution analyzing the effectiveness of steroid therapy as initial therapy for acute GVHD in patients who received HSCT in the 1990s. We observed a response to therapy in 55% of patients and a durable CR in 35% of patients. These results are similar to those observed in the 2 largest previously reported series, primarily consisting of matched sibling donor recipients who received transplants in the late 1970s and 1980s [1,2].

Few demographic or clinical factors were statistically predictive of a response to steroid therapy of GVHD. Related donor recipients and HLA-matched URD recipients had similar overall response rates (59% versus 58%) and 1-year survival rates (58% and 53%). In contrast, patients who received HLA-mismatched URD grafts responded less frequently (46%), and their projected 1-year survival rate (44%) was lower. This result differs from an earlier study reported from our institution that showed a poorer response to GVHD therapy in all URD recipients [4]. In this earlier study, 42 patients with acute GVHD after HLA-matched (29%) or HLA-mismatched (71%) URD BMT from 1985 to 1990 were treated with a prednisone

Table 6. *Clinical Factors Associated with 1-Year Mortality in Acute GVHD: Multivariate Analysis*

Grading System and Factor	Relative Risk of Death (95% CI)	*P*
Minnesota		
Type of donor		
Related	1.0	
Matched unrelated	1.3 (0.9-1.9)	.10
Mismatched unrelated	1.8 (1.3-2.6)	<.01
GVHD prophylaxis		
Other*	1.0	
T-cell depletion	1.4 (1.0-2.1)	.04
Age, in decades	1.2 (1.1-1.3)	<.01
Initial grade of GVHD		
I-II	1.0	
III-IV	1.5 (1.0-2.2)	.05
Consensus		
Type of donor		
Related	1.0	
Matched unrelated	1.3 (0.9-1.9)	.10
Mismatched unrelated	1.8 (1.3-2.6)	<.01
GHVD prophylaxis		
Other*	1.0	
T-cell depletion	1.4 (1.0-2.1)	.04
Age, in decades	1.2 (1.1-1.3)	<.01
Initial grade of GVHD		
I-II	1.0	
III-IV	1.5 (1.0-2.2)	.05
IBMTR		
Type of donor		
Related	1.0	
Matched unrelated	1.3 (0.9-1.8)	.10
Mismatched unrelated	1.8 (1.2-2.5)	<.01
GVHD prophylaxis		
Other*	1.0	
T-cell depletion	1.4 (1.0-2.1)	.04
Age, in decades	1.1 (1.0-1.2)	<.01
Initial grade of GVHD		
A-B	1.0	
C-D	1.4 (1.1-1.9)	<.01

*CSA, MTX, and/or tacrolimus.

regimen similar to that in the present study. Overall response to steroids was observed in only 24% of patients and CR in 21% of patients [4]. The improved response rates to GVHD therapy in this present study may be due in part to advancements in supportive care. These advancements may also explain our finding of improved response to therapy in patients undergoing transplantation in more recent years.

The number of organs involved in GVHD was not predictive of response to therapy. Patients with lower GI involvement, especially in combination with skin involvement, responded less often. We have previously reported a higher likelihood of response to steroids when GVHD is limited to the GI tract [5]. In addition, we have previously observed that liver and/or cutaneous GVHD involvement were independent predictors of poor response [2].

Recipients of T-cell–replete grafts had a higher probability of survival at 1 year than did recipients of T-cell–depleted grafts. A similar finding of improved survival in recipients of T-cell–replete grafts was observed at our institution in a recent analysis of the response to equine antithymocyte globulin (ATG) for steroid-resistant acute GVHD [22].

The IBMTR severity index was developed in 1997 as an objective GVHD grading system [8] with the intent to improve prognostic capabilities compared to the Glucksberg system [23]. At the University of Minnesota, we use a modified Glucksberg grading system that incorporates upper GI GVHD [3,7]. The Minnesota and Consensus GVHD grading systems are similar except for the liver and lower GI staging criteria for grades III and IV GVHD. The IBMTR index is the most different and tends to give a higher GVHD score for a given combination of GVHD stages, resulting in a different distribution of initial GVHD scores. In this study, a higher proportion of patients graded by the IBMTR severity index were categorized as having severe (grades C or D) GVHD (43%) than were patients graded according to the Minnesota or Consensus systems (13% with grades 3 or 4). Initial GVHD grade was not predictive of response to prednisone therapy, except for patients with IBMTR index B or C, who were more likely to achieve overall improvement. With each grading system, severe GVHD and poor response to therapy were associated with lower probability of survival. The Minnesota and IBMTR grading systems better discriminate between initial GVHD grade and survival. Although no GVHD grading system appears superior, the significant discrepancy in assigned grade for a given stage(s) of GVHD is important to note, especially when comparing outcomes of GVHD trials using different GVHD grading systems.

Despite many advances in the past decade in the management of complications related to HSCT, treatment of acute GVHD remains suboptimal. Although a subset of patients may achieve a durable response with steroids, new approaches to GVHD prophylaxis and treatment are needed.

ACKNOWLEDGMENTS

The authors thank the nurses, nurse coordinators, and physicians who cared for these patients and their families.

REFERENCES

1. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood*. 1990;76:1464-1472.
2. 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.
3. Weisdorf DJ, Snover DC, Haake R, et al. Acute upper gastrointestinal graft-versus-host disease: clinical significance and response to immunosuppressive therapy. *Blood*. 1990;76:624-629.
4. Roy J, McGlave PB, Filipovich AH, et al. Acute graft-versus-host disease following unrelated donor marrow transplantation: failure of conventional therapy. *Bone Marrow Transplant*. 1992;10:77-82.
5. Hings IM, Severson R, Filipovich AH, et al. Treatment of moderate and severe acute GVHD after allogeneic bone marrow transplantation. *Transplantation*. 1994;58:437-442.
6. Cragg L, Blazar BR, Defor T, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2000;6:441-447.
7. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
8. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR severity index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol*. 1997;97:855-864.
9. Davies SM, Wagner JE, Shu XO, et al. Unrelated donor bone marrow transplantation for children with acute leukemia. *J Clin Oncol*. 1997;15:557-565.
10. McGlave PB, Shu XO, Wen W, et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. *Blood*. 2000;95:2219-2225.
11. Ramsay NK, Kim TH, McGlave P, et al. Total lymphoid irradiation and cyclophosphamide conditioning prior to bone marrow transplantation for patients with severe aplastic anemia. *Blood*. 1983;62:622-626.
12. McGlave P, Arthur D, Haake R, et al. Therapy of chronic myelogenous leukemia with allogeneic bone marrow transplantation. *J Clin Oncol*. 1987;5:1033-1040.
13. Kersey JH, Weisdorf D, Nesbit ME, et al. Comparison of autologous and allogeneic bone marrow transplantation for treatment of high-risk refractory acute lymphoblastic leukemia. *N Engl J Med*. 1987;317:461-467.
14. Kim TH, McGlave PB, Ramsay N, et al. Comparison of two total body irradiation regimens in allogeneic bone marrow transplantation for acute non-lymphoblastic leukemia in first remission. *Int J Radiat Oncol Biol Phys*. 1990;19:889-897.
15. Barker JN, Davies SM, DeFor T, et al. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood*. 2001;97:2957-2961.
16. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. *Blood*. 1996;88:795-802.
17. Hings IM, Filipovich AH, Miller WJ, et al. Prednisone therapy for acute graft-versus-host disease: short- versus long-term treatment: a prospective randomized trial. *Transplantation*. 1993;56:577-580.

18. Snedecor G, Cochran W. *Statistical Methods*. 8th ed. Ames, Iowa: Iowa State University Press; 1989.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
20. Le C. *Applied Survival Analysis*. New York, NY: John Wiley & Sons; 1997.
21. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data*. New York, NY: John Wiley; 1980.
22. MacMillan ML, Weisdorf DJ, Davies SM, et al. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8:40-46.
23. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974; 18:295-304.