Treatment of Moderate/Severe Acute Graft-Versus-Host Disease After Allogeneic Bone Marrow Transplantation: An Analysis of Clinical Risk Features and Outcome

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We have analyzed the long term outcome of 197 patients who were treated for grade II to IV acute graft-versus-host disease (GVHD) following histocompatible allogeneic bone marrow transplantation (BMT). Of 469 recipients of sibling donor allografts performed at our center between January, 1979 and October, 1987, 197 patients (42%) developed ≥ grade II acute GVHD at a median of 38 days (range 9 to 98 days) post-BMT. After treatment with corticosteroids (n = 160) or other immunosuppressive therapies (n = 37), 72 patients (41% ± 8%; 95% confidence interval [CI]) achieved complete and continuing resolution of acute GVHD after a median of 21 days of therapy. Sixty-one patients required additional immunosuppressive therapy with high dose methylprednisolone, antithymocyte globulin (ATG)/steroids, or other therapies because of refractory or progressive symptoms of acute GVHD. Seven of these 61 patients eventually obtained complete and continuing remission after 13 to 57 days (median 50) of secondary treatment. The overall rate of chronic GVHD was 70% ± 16%; 95% CI following grade II to IV acute GVHD. Twenty-five of the 197 patients never developed chronic GVHD, resulting in a Kaplan-Meier projection of 30% ± 8% (95% CI) cure of moderate/severe acute GVHD. Analysis of clinical features associated with complete response (CR) to acute GVHD therapy identified more favorable responses to therapy in patients without either liver or skin involvement, patients with acute lymphoblastic leukemia, and donor/recipient pairs other than male patients with female donors. Older recipient age was not associated with more resistance to GVHD treatment. CR to GVHD treatment was associated with significantly better 5-year survival: 51% ± 14% versus 32% ± 11% for patients with therapy resistant acute GVHD ($P = .004$). GVHD was a major contributing cause of death in 49 of the 90 patients who died and was often complicated by infection or interstitial pneumonitis. Control of acute GVHD through immunosuppressive therapy did not affect the risk of leukemic relapse after transplantation.

DESPITE THE SUBSTANTIAL frequency and morbidity of acute graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation (BMT), surprisingly little critical literature is available to assess the impact of acute GVHD on survival and to define more appropriate techniques for its management.[1,2] Corticosteroids, antithymocyte globulin (ATG), and more recently, cyclosporine have been the mainstays of therapy, although anti-T cell monoclonal antibodies (MoAbs) or immunotoxins have been used as well.[3-10] Most reports, however, have focused on short term responses to therapy, and have not addressed the need for continuing immunosuppressive therapy, the required intensity and duration of therapy, and the impact of complete and continuing resolution of GVHD on overall survival.

To assess the overall impact of intensive immunosuppressive therapy for acute GVHD, we have retrospectively analyzed the clinical outcomes and complications for recipients of histocompatible allogeneic BMT at the University of Minnesota and who have developed moderate to severe (grade II to IV) acute GVHD.

PATIENT POPULATION AND METHODS

Through review of the prospectively collected records of the University of Minnesota Bone Marrow Transplant Data Base, all patients transplanted between January, 1979, and October, 1987, were included (UPN 77-797). All patients included in this analysis have been followed for a minimum of 1 year post-BMT. During this period, 469 patients received an allogeneic transplant from a matched sibling donor, from which a subset of 197 allogeneic recipients who developed grade II or greater acute GVHD were identified as the subjects for this analysis.

Characteristics of the patients and their GVHD prophylaxis are shown in Table 1. All the patients had histocompatible sibling donors and received prophylaxis against acute GVHD including either: methotrexate alone; methotrexate, horse antithymocyte globulin (ATG) and prednisone[11]; ex vivo T-lymphocyte depletion[12,13]; and other GVHD prophylaxis methods that included methotrexate/cyclosporine/prednisone; methotrexate/OKT3/prednisone; and other variant regimens.[1,14] Details of the conditioning regimens used and supportive care techniques for transplantation have been previously reported.[15-17]

Acute GVHD was diagnosed clinically and confirmed histologically in 98% of skin GVHD, 90% of intestinal GVHD, and 47% of liver GVHD. Symptoms of acute GVHD were graded by standard clinical criteria.[18] The term "grade" of GVHD refers to clinical (not histologic) grade throughout this report. In addition, 25 patients with nausea, vomiting, and anorexia had gastroduodenal acute GVHD confirmed by endoscopic biopsy. They were diagnosed as Grade II GVHD upper gastrointestinal (UGI), though they had no lower GI, hepatic, or significant cutaneous disease and would otherwise have been grade 0 (n = 9) or grade I (n = 16) GVHD.[1,18,19] These patients were treated with systemic immunosuppressive therapy just as other patients with acute GVHD.

Patients were assigned primary therapy for acute GVHD according to treatment protocols in force at the time of transplantation,

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Submitted July 31, 1989; accepted October 16, 1989.

Supported in part by NIH Grant No. P01 CA21737 and by the Bone Marrow Transplant Research Fund.

J.K. is a recipient of an Outstanding Investigator Award (CA49721) from the National Cancer Institute.

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0006-4971/90/7504-0007$3.00/0

Table 1. Clinical Features of Patients with Grade II or Greater Acute GVHD

Features	N (%)*
Male:female ratio	119:78 (60:40)
Male donor/male recipient	58 (29)
Male donor/female recipient	50 (25)
Female donor/male recipient	61 (31)
Female donor/female recipient	28 (14)
Age median (range), yrs	27 (0.9–53.0)
Diagnosis	
Aplastic anemia	24 (12)
ANLL†	47 (24)
ALL‡	32 (16)
CML	75 (38)
Other leukemia§	6 (3)
Other malignancy	7 (4)
Immune deficiency; metabolic disease	6 (3)
GVHD prophylaxis	
Methotrexate/ATG/prednisone	106 (54)
Methotrexate	32 (16)
Ex vivo T-lymphocyte depletion	31 (16)
Other‖	28 (14)

*Percent of patients with ≥ Grade II to IV acute GVHD (n = 197).

†ANLL: 43 in remission, 4 in relapse at BMT.

‡ALL: 29 in remission, 3 in relapse.

§Includes 4 patients with myelodysplastic syndrome, 2 with undifferentiated leukemia.

‖Includes one patient who received no GVHD prophylaxis.

which included: prednisone 60 mg/m^2/d with a slow tapering schedule over 15 weeks (n = 151); or prednisone 60 mg/m^2/d with variant nonprotocol tapering schedules (n = 9). Also used as primary therapy were: high dose methylprednisolone (30 mg/kg intravenously [IV] twice a day for 5 days; n = 8 as primary therapy) and other therapies, including cyclosporine A; anti-T cell immunotoxins, or anti-lymphocyte globulin (n = 29). Nine patients received ATG/prednisone (ATG 15 mg/kg twice a day for 5 days plus prednisone 40 mg/m^2/d, 38 received high dose methylprednisone, and 14 received other regimens as secondary therapy.

Complete response (CR) was defined as the resolution of all symptomatology of acute GVHD before the onset of chronic GVHD (cGVHD). Patients were censored at death, relapse, second BMT, or at the onset of cGVHD in analyses of time to CR. Progression of acute GVHD that required additional therapy was defined as a failure of the initial treatment. Transient or partial responses were distinguished from complete responses. After initial improvement, clinical recurrence of acute GVHD that resolved following additional therapy was recorded as a CR at the time of complete and continuing resolution of all acute GVHD symptoms. Analyses of outcome relating to initial grade of acute GVHD at onset of systemic therapy excluded 10 patients with initial grade I GVHD who later progressed to ≥ grade II disease but received no systemic therapy. Nine patients were unevaluable for CR because of death (n = 3), relapse (n = 2), or cGVHD (n = 4) occurring within 14 days of initial GVHD treatment. Following CR, all but 5 patients were observed for a minimum of 14 days to 86 months (median 7 months) while still at risk for recurrence of acute GVHD. Patients were considered evaluable for cGVHD (n = 142), excluding only those who either died, relapsed, or had a second transplant before day +150.

Statistical analyses were performed using BMDP-83 software (BMDP Statistical Software Inc, Los Angeles, CA) and standard statistical methods. The Kaplan-Meier product limit method was used to evaluate CR and cGVHD with 95% confidence limits derived from the standard errors and time-dependent covariate analysis for nonbaseline characteristics.[20] Differences between groups were assessed with the Mantel-Cox test statistic. Multivariate analysis was performed using the Cox model using known or suspected covariates in a stepwise-multivariate fashion.[21] Factors (one or more) contributing to cause of death were assigned using all available clinical, microbiologic, and autopsy data and were analyzed in association with a CR to acute GVHD using a Chi-square statistic.

RESULTS

Response to initial immunosuppressive therapy. Of the 469 eligible BMT recipients, 197 developed grade II or greater acute GVHD between 9 and 98 days posttransplant (median 38 days). Of these 197, 107 patients had been treated with topical corticosteroids for limited cutaneous GVHD before ≥ grade II disease was documented and systemic therapy started. Overall, 72 of the 197 patients (41% ± 8%; 95% confidence interval [CI]) had a CR to their initial immunosuppressive therapy for acute GVHD after 1 to 78 days of treatment (median, 21 days). Sixty-one patients failed to achieve CR and progressed to require secondary immunosuppressive therapy after 1 to 54 days of treatment (median, 11 days). Sixty-four other patients were censored from analysis of CR because of death before achieving CR (n = 11), development of chronic GVHD before CR of acute GVHD (n = 45), leukemic relapse (n = 7), or a second marrow infusion (n = 1) before CR was achieved.

The response to therapy for 160 patients who received prednisone 60 mg/m^2/d was similar to the group as a whole. Fifty-eight of these 160 (40% ± 8%; 95% CI) achieved CR after 1 to 78 days (median, 22 days) of treatment while 57 patients progressed to require secondary immunosuppressive therapy, 5 died, 6 had leukemic relapse, 1 had a second transplant, and 33 developed cGVHD before a CR to acute GVHD developed.

Clinical features associated with CR. Various pretransplant clinical features were examined for their association with a clinical CR to acute GVHD therapy (Table 2). Patient age was not an important factor in predicting response to the immunosuppressive therapy for acute GVHD. Adults ≥18 years and children less than 18 had similar responses to initial treatment, with 43% of adults and 36% of children achieving CR ($P = .42$). Similar results were observed in the subset receiving prednisone alone for initial treatment (not shown).

The age of the bone marrow donor was not predictive of response to GVHD with adult donors ≥18 years associated with an acute GVHD CR in 43% of the recipients and child donors less than 18 years associated with a CR in 37% ($P = .77$). Recipient gender did not affect the likelihood of CR, nor did donor/recipient sex match, while donor sex was important. Female donors, especially with male recipients, were associated with a significantly lower likelihood of CR ($P = .02$).

The immunosuppressive technique used for GVHD prophylaxis did not predict eventual responsiveness of acute GVHD to immunosuppressive therapy in that GVHD after meth-

Table 2. Clinical Risk Features: Association with Complete Response to Acute GVHD Therapy

Features (N)	Complete Response (% ± 95% CI)	Probability
Overall (197)	41 ± 7.6	
Treatment with prednisone 60 mg/(mol/L)^2/d (160)	40 ± 8	
Recipient Age		
≥18 years (146)	43 ± 9	$P = .42$
<18 (51)	36 ± 14	
Donor Age		
≥18 (145)	43 ± 9	$P = .77$
<18 (52)	37 ± 14	
Recipient Sex		
M (119)	40 ± 10	$P = .61$
F (78)	43 ± 12	
Donor Sex		
M (108)	51 ± 11	$P = .02$
F (89)	31 ± 10	
Donor/Recipient Sex		
Match (86)	48 ± 11	$P = .22$
Male recipient/male donor (58)	54 ± 14	$P = .10$ overall
Female recipient/female donor (28)	37 ± 18	
Mismatch (111)	36 ± 10	
Male recipient/female donor (61)	27 ± 12	Male recipient/female donor v other, $P = .03$
Female recipient/male donor (50)	47 ± 16	
Primary Diagnosis		
ALL (32)	60 ± 19	ALL v others, $P = .03$
ANLL (47)	38 ± 15	ALL v other leukemia, $P = .06$
CML (75)	41 ± 12	
Aplastic anemia (24)	23 ± 18	
GVHD Prophylaxis		
Methotrexate/ATG/Prednisone (116)	42 ± 10	$P = .28$ overall
Methotrexate* (32)	28 ± 16	
T-lymphocyte depletion* (31)	63 ± 21	
Other (27)	37 ± 19	

Kaplan-Meier projections of CR rates for the patient subgroups shown. *P* values reflect Mantel Cox tests of significance in univariate analysis.
*P = not significant for individual comparisons of Methotrexate or T-lymphocyte depletion versus any other group.

otrexate/ATG/prednisone, methotrexate alone, T-lymphocyte depletion, or other prophylactic regimens had similar CR rates overall.

Patients undergoing transplantation for different diagnoses were treated similarly, but had differing responses to immunosuppressive treatment. GVHD in 32 patients with acute lymphoblastic leukemia (ALL) was significantly more responsive than GVHD in all other patients ($P = .03$) or in all other patients with leukemia (n = 128; $P = .06$).

In performing this retrospective analysis, we recognized the potential for change in clinical practices (including earlier diagnosis, more prompt recognition of disease progression, better diagnosis and therapy of opportunistic infections, etc) that could measurably affect the outcome of acute GVHD therapy. We analyzed, therefore, the effect of the year of BMT (1979 to 1987) on likelihood of achieving CR. Though there was substantial year-to-year variability (CR rates ranged from 18% to 67% in different years), there was overall a modest but not significant trend favoring an increased likelihood of achieving CR in more recent years ($P = .16$).

To assess any possible effect of more experienced observation leading to more prompt diagnosis of GVHD in recent years, we evaluated the day of onset and grade of acute GVHD at initial treatment over this time period. Over the 9 years of the study, at the initial diagnosis of acute GVHD, 72% of patients had grade II, 22% had grade III, and 5% had grade IV disease when systemic therapy was initiated. Though the number of patients at each grade varied from year to year, overall there was no trend suggesting a change in either the onset or the severity of GVHD over time.

The initial grade of GVHD was statistically significant in predicting the likelihood of achieving CR. As shown in Table 3, patients with Grade II GVHD at diagnosis were significantly more likely to achieve a continuing CR than patients with more advanced GVHD ($P = .002$). We next assessed the responsiveness of acute GVHD in differing organs. As shown in Table 3, the occurrence of either hepatic ($P = .0001$) or cutaneous ($P = .06$) GVHD was associated with a low likelihood of CR to immunosuppressive therapy. In contrast, patients with gastrointestinal (GI) GVHD had a similar CR rate as those with no GI involvement. The group with GI GVHD included 51 patients with upper GI, but not lower GI GVHD, 33 with lower, but not upper GI GVHD, and 12 patients with both upper and lower GI GVHD. UGI involvement with or without lower GI was significantly associated with CR ($P = .002$). Finally, acute GVHD involving only a single organ (versus two or more) was significantly more likely to result in a CR to therapy, as well.

Because these data suggested the importance of multior-

Table 3. Response of Acute GVHD to Therapy

	N	Complete Response (% ± 95% CI)/Probability
Initial grade of acute GVHD*		
Grade II	(136)	47 ± 9/P = .002 Grade II v III–IV
Grade III	(42)	21 ± 13
Grade IV	(9)	0
Organ involvement with acute GVHD†		
Skin GVHD	(158)	39 ± 8/P = .06
No skin involved	(39)	53 ± 19
GI	(96)	45 ± 11/P = .41
No GI	(101)	39 ± 11
Liver	(54)	15 ± 10/P = .0001
No liver	(143)	51 ± 9
No. organs involved		
1 organ GVHD‡	(99)	55 ± 11/P = .0007
2 or 3 organs	(98)	29 ± 10

Kaplan-Meier projections of CR rates for the patient subgroups shown. P values reflect Mantel Cox tests of significance in univariate analysis.

*Ten patients with ≥ grade II GVHD who initially received no systemic immunosuppressive therapy are excluded.

†Organ involvement at initial therapy. Organ groupings are not mutually exclusive. P values reflect the stated comparison (eg, skin GVHD v no skin involvement).

‡Includes 66 with skin only, 26 with GI only, 7 with liver only.

gan involvement in addition to organ severity, we tested an overall GVHD organ Stage Score as a predictor of response. This overall Stage Score represented the sum of each acute GVHD organ stage (0 to 4) plus 1 point for UGI and thus had a maximum possible score of 13 (0 to 4 in three organs plus UGI). In univariate analysis with this Stage Score measured as a continuous variable, this score was a significant predictor of CR with each additional score point at initial GVHD therapy associated with 0.66 lower likelihood of achieving CR ($P < .0001$).

These clinical factors relevant to the likelihood of achieving CR were then analyzed in a stepwise multivariate analysis. As shown in Table 4, the absence of any liver GVHD was the most significant independent factor associated with CR. Similarly, patients with ALL, those without any skin involvement, and those donor/recipient combinations other than male patients with female donors were significantly and independently associated with more responsive acute GVHD. Notably, neither the overall GVHD grade nor patient age was independently statistically significant in this analysis. However, if the overall Stage Score (described above) was added to the model, it was the most powerful independent predictor of CR.

Table 4. Clinical Factors Associated with Complete Response in Acute GVHD: Multivariate Analysis

Favorable Factor	Relative Likelihood of CR (95% CI)	P
No liver involvement	4.1 (1.8–9.0)	<.0001
ALL v other diagnosis	2.5 (1.4–4.6)	<.003
No skin involvement	2.3 (1.3–4.1)	<.005
Recipient: donor match other than male:female	1.8 (0.95–3.3)	<.07
Initial GVHD grade*	—	<.14
Recipient age (older)	—	<.15

Cox model multivariate analysis of clinical factors associated with CR to therapy for acute GVHD. Factors important in univariate analysis ($P < .10$) along with patient age were added to the model in stepwise fashion. Shown are the favorable factors tested and the associated relative risks and 95% confidence intervals.

*Grade II v III and IV.

Secondary therapy for acute GVHD. Sixty-one of the 197 patients (32% ± 7%, 95% CI) had either inadequate initial responses or progressive acute GVHD and received secondary, more intense therapy for acute GVHD, including ATG/steroids (n = 9), high dose methylprednisolone (n = 38), or other therapies (n = 14). Secondary therapy for acute GVHD was initiated 1 to 54 (median, 10) days after initial treatment for acute GVHD. Of these 61 patients, 7 had a CR, 23 developed chronic GVHD before CR, 30 died, and one received a second transplant before CR. By Kaplan-Meier projection, 39 ± 28% (95% CI) developed a CR to secondary treatment after 13 to 57 (median, 50) days of treatment. Of these patients, 24 had grade II acute GVHD at the time of secondary therapy, 21 had grade III, 15 had grade IV, and 1 had extensive, but ungraded cutaneous involvement. CR developed in four patients with grade II, two with grade III, and one with grade IV acute GVHD at the time of secondary therapy. Of the 160 whose initial treatment for acute GVHD was prednisone 60 mg/m^2/d, 57 required secondary treatment, and 7 of 57 achieved a CR resulting in a product limit estimate of 41 ± 28% (95% CI) CR rate in this subgroup. Because of particularly frequent competing hazards (ie, death, cGVHD), which censor patients in these analyses of secondary therapy, the CR rate should be interpreted cautiously.

Overall, 45 patients received high dose methylprednisolone for extensive acute GVHD, including 7 who received this as initial therapy and 38 as secondary therapy for acute GVHD. Four of these patients achieved CR after 47 to 57 days of treatment. This high dose methylprednisolone regimen resulted in a Kaplan-Meier projected CR rate for all 45 patients of 26 ± 23% (95% CI).

Chronic GVHD. cGVHD developed in 97 of the 142 patients who remained at risk for cGVHD (by Kaplan-Meier projection, 70 ± 8%; 95% CI) between 6 and 596 days (median, 67 days) after initial treatment for acute GVHD. Censored patients include: 48 who died, 22 who had leukemic relapse, and 5 who had a second BMT before developing cGVHD. A higher clinical grade of acute GVHD was more frequently followed by cGVHD. Analyzed by initial grade of acute GVHD, 68% ± 10% of patients with grade II, 82% ± 14% of grade III, and 100% of patients with grade IV GVHD developed cGVHD ($P = .04$, Grade II versus III-IV).

Twenty-five of the 197 patients achieved a CR and subsequently never developed any cGVHD. These patients (20 with initial grade II and 5 with grade III acute GVHD) continued GVHD-free, thus resulting in a Kaplan-Meier projection of a 30% ± 8% permanent cure of this moderate/severe acute GVHD.

Survival. Of the entire group of 197 patients, 84 are alive between 1 and 8.4 years with a Kaplan-Meier projected estimate of 37% ± 8% (95% CI) survival at 5 years after

initiation of treatment for acute GVHD. One hundred thirteen have died between 3 days and 5.6 years after GVHD therapy. Survival rates for the 160 recipients of prednisone as initial GVHD therapy were similar with 35% ± 9% surviving. Survival after secondary GVHD therapy was somewhat worse. Of the 61 patients who received secondary therapy for GVHD after failing initial treatment, only 14 of 61 are alive between 1.3 and 6.9 years later with a projected survival rate of 23% ± 11% at 5 years.

Complete response of acute GVHD was an important predictor of survival. Time dependent analysis of the effect of acute GVHD CR on survival showed that patients achieving CR had a significantly better survival compared with those not achieving CR (51% ± 14% survival after CR versus 32% ± 11%, $P = .004$; Fig 1). Similarly, in patients treated with prednisone alone for initial treatment, achievement of CR in time-dependent analysis was associated with a significantly reduced mortality (relative risk of death .58; $P = .02$).

Patients with a lower maximum grade of acute GVHD had better long term survival. As shown in Fig 2, in the comparison groups 49% ± 7% with no acute GVHD and 49% ± 16% with maximum Grade I GVHD are long-term survivors, while 45% ± 12% of patients with grade II and 38% ± 11% with grade III acute GVHD survive between 10 months and 8 years after initial therapy for GVHD. Only 11% ± 12% of patients with grade IV disease survive long term ($P < .001$). No significant differences in survival between groups with grade O to III GVHD are noted.

Despite this adverse impact of advanced acute GVHD on survival, cGVHD had little overall effect. For patients with CR to acute GVHD therapy, using cGVHD as a time-dependent covariate, the development of chronic GVHD had no significant adverse effect on survival. In these patients with responding acute GVHD, cGVHD was associated with a relative risk of death of only .65 compared with patients without cGVHD ($P = .44$).

Causes of death. The favorable impact of achieving CR on survival was reflected in the analysis of patients' cause of death. For patients failing to achieve CR, GVHD (acute or chronic) was a major contributing cause of death in 49 of the 90 patients who died. Of patients who died after achieving CR, only 5 of 33 deaths were associated with GVHD as a contributing cause of death, usually complicated by infection ($P < .0001$). Patients dying without CR most often also had infection (fungal, viral, or bacterial) as an additional contributing cause of death. Of those achieving CR, 18 of 33 died of infection, while in patients without CR, significantly more (60 of 80) died of infection ($P = .03$). Interstitial pneumonitis, however, was not significantly differently observed as a contributing cause of death in patients with or without CR to GVHD. Of CR patients, 13 of 33 deaths were associated with interstitial pneumonitis while 44 of 80 deaths in patients without CR were due to pneumonitis ($P = .13$).

Among 128 patients with leukemia, relapse was a major contributing cause of death more frequently observed in patients achieving a CR to GVHD. Eighteen of 33 deaths after GVHD CR were due to leukemic recurrence, while only 12 of 80 patients not achieving CR died of leukemia ($P < .001$). However, within the leukemic subgroup, a time dependent analysis of the effect of achieving a CR on subsequent leukemia relapse showed no significant impact of CR on subsequent relapse risk ($P = .34$).

DISCUSSION

Successful therapy of acute GVHD most often includes intensive immunosuppressive treatment to halt the ongoing attack on host tissues and must be designed to protect the host from further immunologic injury, to facilitate the development of immunologic tolerance, and to allow the reconstitution of host defenses against opportunistic infection. This analysis, using a definition of CR requiring complete and continuing response to immunosuppressive therapy for moderate/severe acute GVHD, shows that despite the intensity of current immunosuppressive treatment, only 40% of patients treated with standard immunosuppressive agents gain complete control of acute GVHD, and only 30% have a long term remission of any GVHD. Overall, more than 70% of those surviving acute GVHD develop cGVHD, which further compromises their recovery from marrow transplantation.

GVHD resistant to initial immunosuppressive treatment was also frequent with nearly one third of patients requiring secondary therapy after a median of only 10 days of primary treatment for acute GVHD. Secondary GVHD treatment

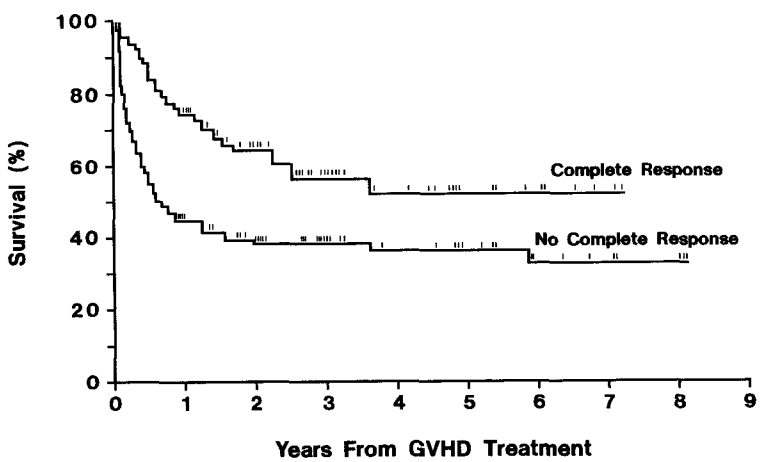

Fig 1. Product limit estimates of survival after therapy for acute GVHD with complete response to therapy as a time-dependent covariate. Tic marks represent patients surviving ($P = .004$).

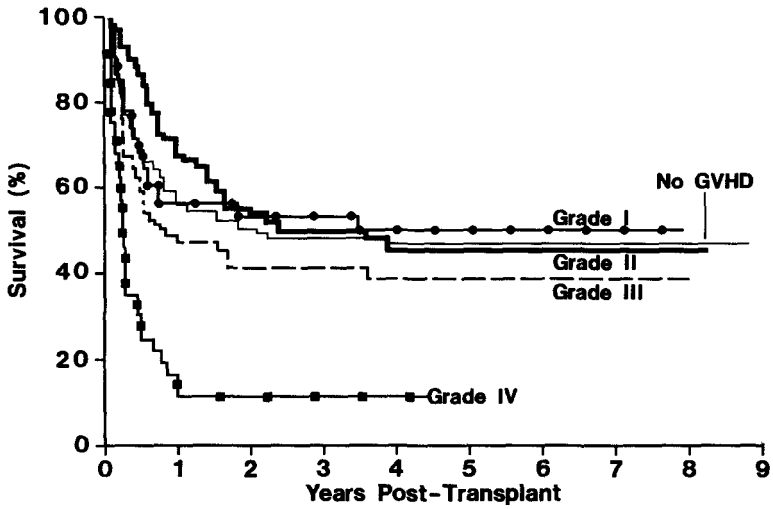

Fig 2. The effect of maximum grade of acute GVHD on survival. Included for comparison are patients with no or mild (Grade I) acute GVHD. No significant differences between grade O to III patients were observed. (Grade IV versus other: $P < .0001$). The curves reflect the following numbers of patients surviving in each GVHD cohort beyond 3 and 5 years post-BMT. 3 years: grade O, 59; I, 17; II, 29; III, 16; IV, 2. 5 years: grade O, 37; I, 11; II, 15; III, 8; IV, 0.

was required for all disease progression, but also for inadequate response to primary treatment of even limited GVHD. More than 75% of the patients who went on to secondary therapy had ≤ grade III GVHD. Responsiveness to secondary therapy was neither predictable nor prompt and was recognized only after 6 to 8 weeks of secondary treatment. Four of the seven secondary CR patients initially had grade II, two had grade III, and only one had grade IV disease, suggesting that initially resistant, but still limited acute GVHD may be more responsive to secondary treatment.

We are encouraged to find that effective therapy for GVHD and the achievement of CR favorably influenced survival with a statistically significant 47% reduction in mortality risk in those patients achieving a CR. Patients dying without CR most often died with GVHD and infection as major contributing causes of death.

Few demographic or clinical factors were statistically predictive of good response to therapy of patients' GVHD. Neither GVHD prophylaxis, patient age, nor donor age were predictive of response to initial therapy of acute GVHD. Perhaps surprisingly, older patients had slightly higher CR rates, given similar therapy and stage of acute GVHD. This tendency for older patients to respond favorably to therapy was also manifest in their responsiveness to secondary GVHD treatment. Of the seven complete responses to secondary therapy, six were adults (25 to 39 years of age). All seven secondary complete responders had received prednisone alone for initial treatment and six of seven received transplants for leukemia.

GVHD, which spared the liver and, less so, the skin, was strikingly associated with greater likelihood of CR to immunosuppressive therapy. Hepatic and/or cutaneous involvement were independent predictors of poor response to therapy and were considerably more important than the overall initial grade of GVHD in predicting CR. UGI involvement was frequently associated with CR, as well. The finding of significantly more responsive acute GVHD in ALL patients was unexpected. The patients with ALL were significantly younger, but had similar recipient/donor sex combinations as well as similar GVHD prophylaxis. The GVHD observed in patients with ALL was also of similar grade and organ involvement and thus ALL appeared as a prominent and independent factor predicting CR. The validity of our observation of ALL as a factor associated with responsive GVHD requires confirmation.

We tested a new and simple parameter, the GVHD organ Stage Score as a predictor of response. This Stage Score, which reflects both the extent and severity of acute GVHD, appeared to be the most powerful independent predictor of complete clinical response to therapy, and in future studies, might be usefully applied as a measure of short-term, transient, or partial responses.

GVHD occurring in recipients (especially males) of marrow from female donors was significantly more resistant to therapy, perhaps reflecting an indirect manifestation of prior alloimmunization in parous female (or transfused) donors which has been reported as a significant risk factor for the development of acute GVHD.[22,23] Alternatively, since this resistant GVHD was more apparent in female donor/male recipient transplants, this may reflect the postulated immune recognition of H-Y antigen or Y chromosome linked alloantigens serving as stimulating factors for the GVHD reaction.[24]

The current data allow us to emphasize several principles in management of acute GVHD. We have observed that at least within the relatively homogeneous group of histocompatible sibling donor allografts, some risk factors for the development of acute GVHD may also predict its ultimate responsiveness to immunosuppressive therapy. If confirmatory analysis from other centers would validate the finding of relatively resistant acute GVHD occurring in patients without ALL or in transplantation from female donors, particularly into male recipients, then these subgroups might be targeted for alternate or more intensive therapies, even at first presentation of even mild acute GVHD. Alternatively, the greater hazards associated with the development of acute GVHD in these subgroups might indicate the need for even more intense immunoprophylaxis against acute GVHD for such patients. Further critical analysis of broad experience in GVHD therapy will be required to assist in these determinations.

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