A Retrospective Analysis of Therapy for Acute Graft-Versus-Host Disease: Secondary Treatment

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We have reviewed results of secondary therapy in 427 patients with acute graft-versus-host disease (GVHD) who did not have a durable satisfactory response after primary treatment. At the beginning of secondary treatment, 320 patients (75%) had rash, 252 (59%) had liver dysfunction, and 228 (53%) had gut dysfunction. Secondary treatment was with glucocorticoids (n = 249), cyclosporine (n = 80), antithymocyte globulin (n = 114), or monoclonal antibody (n = 19) either singly (n = 390) or in combination (n = 37). Parameters of GVHD severity were recorded weekly, and responses were determined according to values at the initiation of tertiary treatment or, for patients without such treatment, using values on day 29 of secondary treatment or the last recorded values before death, whichever occurred first. Minimal criteria for improvement or deterioration were defined for each organ, but no attempt was made to define liver or gut outcome if another complication such as venocclusive disease or infectious enteritis was present. Improvement or resolution of GVHD in the respective organ was seen in 45% of patients with skin disease, 25% of patients with evaluable liver disease, and in 35% of patients with evaluable gut disease. Overall complete or partial responses were seen in 40% of patients. The highest complete response rate with secondary therapy (23%) was seen when GVHD recurred during the taper phase of primary glucocorticoid treatment and was managed by increasing the dose of glucocorticoids. Multivariate analyses were performed to identify patient, disease, or treatment factors associated with likelihood of complete response or overall improvement. A similar analysis was performed to identify covariates associated with time to treatment failure (defined as initiation of tertiary therapy or death not due to relapse of malignancy). Severe dysfunction in the skin, liver, and gut at the beginning of treatment was associated both with a decreased likelihood of complete response and an increased treatment failure rate. The times to treatment failure and the proportions of patients in various response categories were similar for primary and secondary treatment, suggesting that the potential efficacy of new immunosuppressive agents for treatment of acute GVHD can be assessed meaningfully in patients who have not responded adequately to initial therapy.

ACUTE GRAFT-VERSUS-HOST DISEASE (GVHD) represents one of the major complications of allogeneic marrow transplantation. Although new combined agent prophylaxis regimens provide good protection against GVHD in most patients transplanted with HLA-identical marrow,[1,2] the risk of GVHD remains high in patients transplanted with HLA-nonidentical marrow or with marrow from an unrelated donor.[3,4] When acute GVHD occurs, it can sometimes be controlled by immunosuppressive treatment with glucocorticoids, antithymocyte globulin (ATG), or cyclosporine.[5-18]

We have reviewed results of therapy in a large number of patients with acute GVHD after allogeneic marrow transplantation. The purpose and goals of this study were to define the natural history of acute GVHD, to determine patient and disease characteristics that influence therapeutic response and survival, to assess treatment factors that influence outcome, and to assess methods for analysis of future treatment trials. Data were collected retrospectively and then analyzed according to predefined criteria using two endpoints, treatment response and time to treatment failure. This approach identified patient, disease, and treatment factors associated with favorable or unfavorable outcome after initial therapy of acute GVHD, and also confirmed that treatment of GVHD remains unsatisfactory.[19] Overall, less than 50% of patients with acute GVHD showed durable improvement after initial treatment. Many patients required secondary treatment, and mortality was high, particularly in those whose disease did not respond.

This experience has impelled the search for more effective immunosuppressive agents that could be used safely for GVHD treatment. Most often, new agents such as monoclonal antibodies (MoAbs)[20-22] and immunotoxins[23] have been tested at first in patients who have not responded adequately to initial treatment. Although these studies have been designed mainly to determine toxicity and safety, they have also sought to assess the potential efficacy of new agents. However, this assessment has been hampered by the lack of published data describing the efficacy of currently available agents when used for secondary treatment of GVHD. For this reason, we have extended our previous analysis to assess the response to secondary treatment in patients who did not respond adequately to primary treatment.

MATERIALS AND METHODS

The results of secondary therapy for acute GVHD were analyzed using methods described previously for the analysis of initial therapy.[19] Salient features of the approach will be summarized here, but full details will not be repeated.

Patients. Records were abstracted and case report forms were prepared for all patients who were given systemic immunosuppressive treatment for acute GVHD of at least grade II severity after a first allogeneic marrow transplant at the Fred Hutchinson Cancer

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Research Center (FHCRC; Seattle, WA) between September 1975 and October 1987.

Secondary treatment. Primary therapy was administered when patients developed clinical evidence of acute GVHD after marrow transplantation. Secondary therapy for GVHD was initiated whenever the attending physician made a change in treatment because the response to primary therapy was less than satisfactory. In general, secondary treatment was started if GVHD was progressive any time after at least 3 days of initial therapy, if unimproving grades III and IV GVHD persisted after at least 7 days of initial therapy, or if unimproving grade II GVHD persisted after at least 14 days of initial therapy. When glucocorticoid dose was increased because of GVHD recurring during pretaper or taper of primary treatment or when ATG therapy was extended beyond the originally prescribed dose, that change was considered to represent secondary therapy. Treatment of chronic GVHD was not considered secondary therapy. For secondary treatment of GVHD, methylprednisolone was generally administered at doses of 2 to 4 mg/kg/d for at least 14 days, and doses were subsequently tapered as allowed by the clinical response. ATG was administered at doses of 15 mg/kg every other day for six doses, and cyclosporine was administered at doses of 3 mg/kg/d intravenously (IV) or 12.5 mg/kg/d orally. Regimens for MoAb treatment have been described elsewhere.[20-22] Methotrexate and cyclosporine administered for GVHD prophylaxis were continued during GVHD treatment unless there was toxicity. Glucocorticoids and cyclosporine administered as primary GVHD treatment were generally continued during secondary treatment unless there was toxicity.

Staging of organ dysfunction. Severity of dysfunction in the skin, liver, and gut at the onset of secondary treatment was categorized in all patients regardless of whether GVHD or other complications accounted for any abnormality. Thus, this categorization does not represent a specific staging of GVHD. For all organs, stage 0 indicates normal function. Skin severity was staged according to the extent of surface involved by rash: grade I, $\leq$25%; grade II, 26% to 50%; grade III, 51% to 75%, grade IV, greater than 75%. Severity of hepatic dysfunction was categorized according to the serum bilirubin concentration: grade I, 2.0 to 2.9 mg/dL; grade II, 3.0 to 5.9 mg/dL; grade III, 6.0 to 14.9 mg/dL; grade IV, greater than 15 mg/dL. Severity of gut dysfunction was categorized according to the volume of diarrhea and the presence of cramps or visible blood in the stool: grade I, diarrhea volume 500 to 999 mL/d; grade II, 1,000 to 1,499 mL/d; grade III, diarrhea volume $\geq$1,500 mL/d or cramps or visible blood; grade IV, simultaneous presence of any two or all three of the criteria for grade III severity. For statistical analysis, a numerical score of 0 to 4 equivalent to the severity stage was assigned for each organ.

Measurements of response. No attempt was made to define response in the liver or gut if a complication other than GVHD was known to be present in the respective organ at any time during secondary treatment, even if there was biopsy evidence of GVHD.[19] Responses were evaluated at the initiation of tertiary treatment or, for patients without such treatment, on day 29 of secondary treatment or at the last weekly observation before death, whichever occurred first. Skin disease was considered improved if there was resolution of rash or decrease of involved surface area by $\geq$25%. Progressive skin disease was defined as an increase in involved surface area by $\geq$25%. Liver disease was considered improved if there was a decrease in serum bilirubin to less than 2 mg/dL for patients with baseline values of 2 to 4 mg/dL, a decrease of $\geq$2 mg/dL for patients with baseline values of 4 to 8 mg/dL, or a $\geq$25% decrease in serum bilirubin for patients with baseline values $\geq$8 mg/dL. Progressive liver disease was defined as an increase of serum bilirubin by $\geq$2 mg/dL for patients with baseline values less than 8 mg/dL or $\geq$25% increase in serum bilirubin for patients with baseline values $\geq$8 mg/dL. Gut disease was considered improved if there was resolution of diarrhea or decrease in the 3-day average stool volume by $\geq$500 mL with clearing of cramps and bleeding if present. Clearing of any cramps and bleeding was considered as evidence of improvement in patients who had diarrhea volumes less than 500 mL but not in patients who had unchanged diarrhea volumes $\geq$500 mL. Progressive gut disease was defined as an increase in the 3-day average stool volume by $\geq$500 mL or the development of new cramps or bleeding. For all organs, assessment of treatment response was made entirely according to clinical criteria regardless of biopsy or autopsy findings.

Overall response categories were determined for each patient, but organs not evaluable because of complications other than GVHD or because of inability to determine response were not considered. Complete response (CR) was defined as resolution of GVHD in all evaluable involved organs with no subsequent additional treatment given for acute GVHD. Partial response (PR) was defined in two ways: as improvement in at least one evaluable organ without deterioration in others, or as resolution of GVHD in all evaluable organs with a requirement for additional treatment because of abnormality persisting in a nonevaluable organ. Mixed response (MR) was defined as improvement in at least one evaluable organ with deterioration in at least one other. Overall progression (P) was defined as deterioration in at least one evaluable organ without improvement in others, while no change (NC) was defined as the absence of any difference sufficient to meet minimal criteria for improvement or deterioration in any evaluable organ after treatment. In some patients, a response

Table 1. Patient Characteristics. Secondary Treatment (n = 427)

Median patient age, years (range)	22 (0.8–58)
Patient sex, n (%)	
Male	265 (62)
Female	162 (38)
Pretransplant diagnosis, n (%)	
Acute nonlymphoblastic leukemia	134 (31)
Acute lymphoblastic leukemia	105 (25)
Chronic myelogenous leukemia	98 (23)
Aplastic anemia	41 (10)
Other	49 (11)
Number of recipient HLA disparities, n (%)	
0*	279 (65)
1	71 (17)
2	57 (13)
3	20 (5)
Prescribed prophylaxis, n (%)	
Methotrexate	232 (54)
Cyclosporine	25 (6)
Methotrexate/cyclosporine	160 (37)
No prophylaxis, T-cell depletion	1 (0.2)
No prophylaxis, unmodified marrow	9 (2)
Supplemental ATG	16 (4)
Supplemental glucocorticoids	13 (3)
Interruption of original prophylaxis, n (%)	222 (52)
Substitution of glucocorticoids as prophylaxis, n (%)	43 (10)

*Twenty-four donors were HLA-phenotypically identical relatives and nine were HLA-phenotypically identical unrelated individuals. All other donors in this category were HLA-genotypically identical siblings.

Table 2. Severity of Organ Dysfunction at Onset of Secondary Treatment

Severity*	Organ		
	Skin (%)	Liver (%)	Gut (%)
0	102 (24)	173 (41)	195 (46)
I	48 (11)	39 (9)	66 (16)
II	57 (14)	69 (16)	31 (7)
III	205 (49)	95 (22)	86 (20)
IV	10 (2)	49 (12)	45 (11)
Missing	5	2	4

*Severity is categorized according to criteria described in Materials and Methods and does not necessarily correspond to GVHD stage: 97 patients had abdominal pain and 52 patients had visible stool blood as reasons for stage III and IV gut severity. Data indicate the numbers of patients in each category. Numbers in parentheses indicate the percent in each category.

category could not be assigned because none of the involved organs could be evaluated.

Statistical analysis. Multivariate logistic regression analysis[24] was used to identify factors associated with response categories. Multivariate proportional hazards regression analysis[25] was used to identify factors associated with time to treatment failure defined as either the initiation of tertiary treatment (ie, any change in therapy made because of lack of satisfactory response) or death not due to relapse of malignancy, whichever occurred first. Covariates considered for the multivariate models included patient characteristics (age, sex, diagnosis, recipient HLA disparity, and cytomegalovirus [CMV] serology), donor characteristics (age, sex, CMV serology), chronology of GVHD and treatment (interval times from transplant to onset of GVHD and primary and secondary treatment, interval time between primary and secondary treatment), severity of organ dysfunction at the beginning of secondary treatment (percent skin involvement, serum bilirubin, gut severity score, sum total severity score for all organs, presence of complications other than GVHD in the liver or gut, creatinine ≥ 2 mg/dL), treatment characteristics (agents used for GVHD prophylaxis, continuity of prophylaxis before GVHD treatment, laminar air flow isolation, and agents administered for primary and secondary GVHD therapy), and calendar year of transplant. Covariates were entered in the model in a step-up progression until the P value for the improvement χ^2 was $> .05$ for all remaining factors not included in the model. All P values are two-sided without adjustment for multiple comparisons. Because of multiple comparisons, P values near .05 should be considered as trends and not as definitive evidence. Relative risks are adjusted for the influence of other factors entered into the final model. Thus, these values estimate the independent incremental risk added by each factor after other factors have been taken into account.

RESULTS

Patient characteristics. Of the 740 patients who received primary systemic treatment for acute GVHD,[19] 427 (58%) were given secondary treatment and 221 (30%) were given tertiary treatment. Demographic characteristics of the patients who received secondary treatment (Table 1) were similar to those of the entire population who received primary treatment.[19] The onset of acute GVHD occurred at a median of 17 days, and primary treatment was initiated at a median of 21 days after transplantation. At the beginning of primary treatment, 355 of the 427 patients (83%) had rash, 216 (51%) had liver dysfunction, and 243 (57%) had gut dysfunction. Primary treatment was with glucocorti-

Table 3. Response to Secondary Treatment of Acute GVHD Categorized by Individual Organs

Involvement and Outcome	Organ (n = 427)		
	Skin	Liver	Gut
Definite involvement	338 [79]	149 [35]	201 [47]
Evaluable	314	118	179
Resolution	97 (31)	20 (17)	53 (30)
Improvement	45 (14)	10 (8)	10 (6)
No change	133 (42)	32 (27)	52 (29)
Progression	39 (12)	56 (47)	64 (36)
Nonevaluable	24	31	22
Early death*	24	5	15
Interference†	0	26	7
Uncertain involvement	3 [1]	146 [34]	83 [19]
Data missing	3	3	5
Other complications presents‡	0	143	78
Uninvolved§	86 [20]	132 [31]	143 [33]

Data indicate the numbers of patients in each category. Numbers in brackets indicate percent of total patients in each category. Numbers in parentheses indicate percent of evaluable patients in each category.

*Early death was defined as occurring within 6 days after beginning treatment for GVHD.

†Interference in the evaluation of liver disease occurred because of a change in renal function, and interference in the evaluation of gut disease occurred because of urinary mixing with stool in situations where there was no other basis for judging outcome (see Materials and Methods).

‡Of the 143 patients not evaluable because of hepatic complications other than GVHD, 89 had venocclusive disease, 44 had viral hepatitis, 6 had bacterial infections or sepsis, 9 had fungal or other infections, and 10 had other pathologic processes. Of the 78 patients not evaluable because of gut complications other than GVHD, 38 had viral enteritis, 24 had bacterial enteritis, 23 had fungal enteritis, and 8 had other pathologic process. Outcome for these patients is described in the text.

§Some organs with normal function at the beginning of treatment subsequently developed abnormality. Hence, the numbers of uninvolved organs in this table are smaller than the corresponding numbers in Table 2.

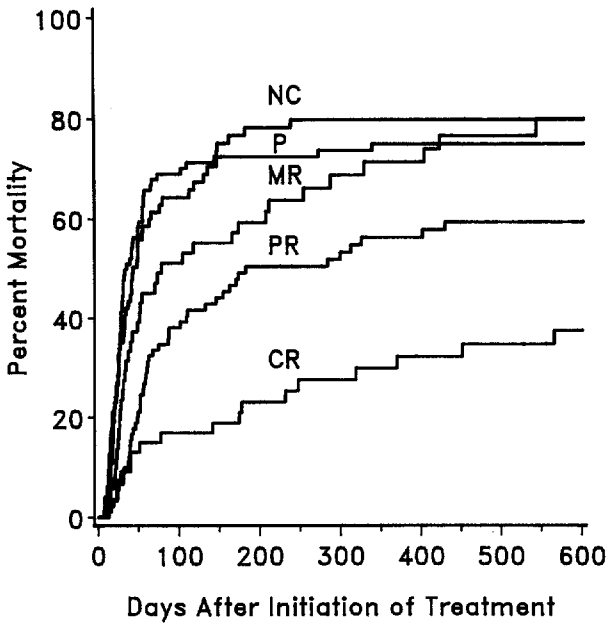

Fig 1. Nonrelapse mortality of patients categorized according to treatment outcome. CR indicates complete response; PR, partial response; MR, mixed response; NC, no change; P, progression ($P < .0001$ for equality among groups). Numbers of patients in each category are given in Table 4. Deaths due to relapse are censored according to the method of Kaplan and Meier.[26]

coids (n = 299), cyclosporine (n = 98), ATG (n = 99), or MoAb (n = 3), either singly (n = 364) or in combination (n = 63). Of the patients treated with glucocorticoids, 150 (50%) had doses tapered after an initial response. At the end of primary treatment, rash was unimproved in 248 (70%) of the 355 patients who had skin involvement at the beginning of primary treatment, hepatic function was unimproved in 96 of 124 patients (77%) with evaluable liver GVHD, and gut symptoms were unimproved in 145 of 226 patients (64%) with evaluable gut GVHD. In addition, 24 patients who had no clinical skin involvement at the beginning of primary therapy developed rash during treatment. After primary treatment, 116 patients (27%) had an overall PR, 62 (15%) had MR, 92 (22%) had NC, 135 (32%) had progression, and 22 (5%) were not evaluable. Secondary treatment was initiated at a median of 37 days after transplantation with a median 12-day interval between primary and secondary treatment. At the beginning of secondary treatment, 75% of patients had rash, 59% had liver dysfunction, and 53% had gut symptoms (Table 2). Renal impairment (creatinine ≥ 2.0 mg/dL) was present in 50 patients (12%), and 22 (5%) were on dialysis when secondary treatment was started.

Organ response to secondary treatment. Secondary treatment consisted of glucocorticoids (n = 249), cyclosporine (n = 80), ATG (n = 114), or MoAb (n = 19), either singly (n = 390) or in combination (n = 37). For a variety of reasons (usually the presence of a complication other than GVHD), outcome could not be evaluated in 60% of the 295 patients with liver dysfunction or in 37% of the 284 patients with gut symptoms (Table 3). Improvement or resolution of GVHD in the respective organ was seen in 45% of patients with skin disease, 25% of patients with evaluable liver disease, and in 35% of patients with evaluable gut disease. Progression of involvement was more likely for liver and gut disease than for skin disease. Among the 143 patients with other posttransplant complications involving the liver, 80 (56%) had moderate or severe (stages II through IV) hepatic dysfunction before secondary treatment for GVHD, and 15% showed improvement in hepatic function after treatment (data not shown). Among the 78 patients with other posttransplant complications involving the gastrointestinal tract, 36 (46%) had moderate or severe (stages III and IV) gut dysfunction before secondary treatment for GVHD, and only 12% showed improvement in gut function after treatment ($P < .01$ compared with patients without other gastrointestinal complications) (data not shown). Improvement rates for skin and liver disease after secondary treatment were comparable to those seen with primary treatment,[19] but the 35% improvement rate for gut disease

Table 4. Overall Response to Secondary Treatment

Agent† (n)	Evaluable	Outcome*				
		CR	CR + PR	CR + PR + MR	NC	P
ATG (94)	79	6 (8)	24 (30)	38 (48)	20 (25)	21 (27)
Cyclosporine (56)	45	6 (13)	13 (29)	20 (44)	15 (33)	10 (22)
Glucocorticoids (219)	181	35 (19)	87 (48)	104 (57)	31 (17)	46 (25)
MoAb (18)	16	0 (0)	7 (44)	9 (56)	5 (31)	2 (13)
Single agents (390)	324	47 (15)	131 (40)	172 (53)	72 (22)	80 (25)
Combined agents (37)	34	8 (24)	17 (50)	21 (62)	5 (15)	8 (24)
Steroids after taper (115)	91	22 (24)	43 (47)	54 (59)	16 (18)	21 (23)
Other patients (312)	267	33 (12)	105 (39)	139 (52)	61 (23)	67 (25)
Overall secondary (427)	358	55 (15)	148 (41)	193 (54)	77 (22)	88 (25)
Overall initial (740)	684	123 (18)	304 (44)	392 (57)	124 (18)	168 (25)

Abbreviations: NE, not evaluable.

*Data indicate numbers of patients in each category. Numbers in parentheses indicate the percent of evaluable patients in each category.

†Results are shown for single agent treatment with ATG, cyclosporine, glucocorticoids, or MoAb; 20 patients received ATG as part of a combined regimen, 23 patients received cyclosporine as part of a combined regimen, 29 patients received glucocorticoids as part of a combined regimen, and 2 patients received MoAb as part of a combined regimen.

Table 5. Factors Associated With CR

Risk Factor*	Relative Risk†	95% CI	P‡
Initial total organ severity score (per unit)	0.72	0.62–0.83	.0001
Use of glucocorticoids for secondary treatment	2.34	1.15–4.75	.019

Abbreviation: CI, confidence interval.

*Risk factors are listed in the order in which they entered the multivariate model.

†Values > 1.0 indicate higher likelihood of CR, whereas values < 1.0 indicate lower likelihood. Relative risks for dichotomous covariates are calculated with reference to patients not having the indicated risk factor. Values for nondichotomous covariates are calculated as the incremental risk per unit indicated in parentheses.

‡Values of *P* resulted from testing the hypothesis that the relative risk was equivalent to 1.0.

after secondary treatment was lower than the 50% improvement rate for gut disease following primary treatment ($P < .01$).

Overall response after secondary treatment. For each patient, an overall response category was defined according to outcome in evaluable organs. We analyzed nonrelapse mortality for patients in each response category as a way of testing the validity of using a nonfixed time point for evaluation and censoring nonevaluable organs (see Materials and Methods). Patients with CR or PR had 2-year nonrelapse mortalities of 38% and 61%, respectively (Fig 1). Two-year nonrelapse mortalities for patients with MR, NC, or P were 77% to 84%. Nonevaluable patients had a 2-year nonrelapse mortality of 79% (not shown). The correlation between response category and subsequent nonrelapse mortality supports the validity of the classification system. Because patients with MR or NC had survival similar to that of patients with progressive disease, it appears that improvement (or the absence of deterioration) in all evaluable organs represents an important indicator of survival in patients given secondary treatment for acute GVHD. The corresponding 2-year nonrelapse mortalities for patients with CR, PR, and MR after primary treatment for GVHD were 31%, 53%, and 58%, respectively.[19] Thus, for patients with equivalent outcome, nonrelapse mortality was higher after secondary treatment than after primary treatment.

Although different secondary treatment agents gave similar improvement rates for individual organs (data not shown), overall responses were better with glucocorticoids than with other single agents ($P < .025$) (Table 4). This difference was not apparent when patients who had recurrent GVHD during the taper phase of primary treatment with glucocorticoids were excluded (data not shown). Thus, the beneficial outcome associated with glucocorticoid treatment occurred only in patients who had GVHD recurring during the taper phase of primary treatment with glucocorticoids. Treatment with combined agents appeared to give somewhat better results than single agents, but the difference was not statistically significant. Overall, 15% of patients had a complete response, 40% showed overall improvement (CR + PR), and 54% showed improvement in at least one organ (CR + PR + MR) (Table 4). These results were remarkably similar to those for initial treatment. The highest CR rate with secondary therapy was seen when GVHD recurred during the taper phase of primary glucocorticoid treatment and was managed by increasing the dose of glucocorticoids either as a single agent or as part of a combined regimen (Table 4) ($P < .02$ compared with other patients).

Multivariate analyses of factors associated with treatment outcome. Multivariate logistic regression analysis was performed to identify factors associated with complete response (Table 5), and a separate analysis was performed to identify factors associated with overall improvement (CR + PR) (Table 6). As an alternative approach, a multivariate proportional hazards regression analysis was used to identify factors associated with time to treatment failure (Table 7) defined either as the initiation of tertiary treatment or death not due to recurrence of malignancy, whichever occurred first. Because of small numbers, patients who received unmodified or T-cell–depleted marrow and no GVHD prophylaxis were excluded from these analyses. Only two factors entered each of the two response models (Tables 5 and 6), whereas six factors entered the model of time to treatment failure (Table 7). One of the factors associated with an increased treatment failure rate also entered one of the response models: severe organ

Table 6. Factors Associated With Overall Improvement (CR or PR)

Risk Factor*	Relative Risk†	95% CI	P‡
Use of glucocorticoids for secondary treatment	1.73	1.10–2.71	.017
Interruption of prophylaxis§	0.62	0.40–0.96	.031

Abbreviation: CI, confidence interval.

*Risk factors are listed in the order in which they entered the multivariate model.

†Values > 1.0 indicate higher likelihood of overall improvement, whereas values < 1.0 indicate lower likelihood. Relative risks for dichotomous covariates are calculated with reference to patients not having the indicated risk factor.

‡Values of *P* resulted from testing the hypothesis that the relative risk was equivalent to 1.0.

§Any decrease from protocol-prescribed doses of posttransplant immunosuppressive medications at any time before initial GVHD treatment was considered an interruption of prophylaxis.

Table 7. Factors Associated With Time to Treatment Failure

Risk Factor*	Relative Risk†	95% CI	P‡
Creatinine ≥ 2.0 mg/dL	2.06	1.44–2.96	.0001
Initial total organ severity score (per unit)	1.15	1.09–1.21	.000001
Hepatic complication other than GVHD	1.90	1.46–2.46	.00001
Patient age (per decade)	1.17	1.05–1.30	.005
Methotrexate prophylaxis	1.46	1.12–1.91	.006
Glucocorticoid substitute prophylaxis	1.51	1.02–2.22	.04

Abbreviation: CI, confidence interval.

*Risk factors are listed in the order in which they entered the multivariate model.

†Values > 1.0 indicate higher likelihood of treatment failure (nonrelapse mortality or initiation of secondary treatment), whereas values < 1.0 indicate lower likelihood. Relative risks for dichotomous covariates are calculated with reference to patients not having the indicated risk factor. Values for nondichotomous covariates are calculated as the incremental risk per unit indicated in parentheses.

‡Values of *P* resulted from testing the hypothesis that the relative risk was equivalent to 1.0.

dysfunction at the beginning of secondary treatment was associated with a decreased likelihood of complete response (Table 5). In keeping with results shown in Table 4, the multivariate analysis confirmed that CR and overall improvement were more frequent in patients given secondary treatment with glucocorticoids as opposed to other agents (Tables 5 and 6). Division of glucocorticoid-treated patients into subgroups according to whether GVHD had recurred during the taper phase of primary glucocorticoid treatment did not improve the models. The presence of a hepatic complication other than GVHD was associated with an increased failure rate not only after secondary treatment (Table 7), but also after primary treatment.[15]

Figure 2 illustrates Kaplan-Meier[26] estimates of the probability of treatment failure according to the presence of renal impairment or hepatic complication other than GVHD and also according to severity of organ dysfunction at the beginning of secondary treatment. Remarkably, the time to failure after secondary treatment in the 427 patients was identical to that seen after primary treatment in the entire group of 740 patients (Fig 2).

DISCUSSION

Considering that secondary therapy for GVHD was initiated because of unsatisfactory response to primary therapy, one might have expected less successful outcomes with secondary treatment compared with primary treatment. In one important regard, this was the case: the respective nonrelapse mortalities for patients with CR, PR, and MR were higher after secondary treatment than after primary treatment.[19] Otherwise, the overall results for secondary therapy of GVHD showed remarkable similarity to those reported previously for primary therapy, whether assessed as treatment response or time to treatment failure. Responses to secondary therapy were particularly favorable among the patients treated with glucocorticoids because of GVHD recurring during the taper phase of primary treatment with glucocorticoids. When this group was excluded, responses to secondary treatment were less favorable than those seen after primary treatment.

In the previous analysis of initial therapy for GVHD, the covariates that entered multivariate models both for response and time to treatment failure were considered to

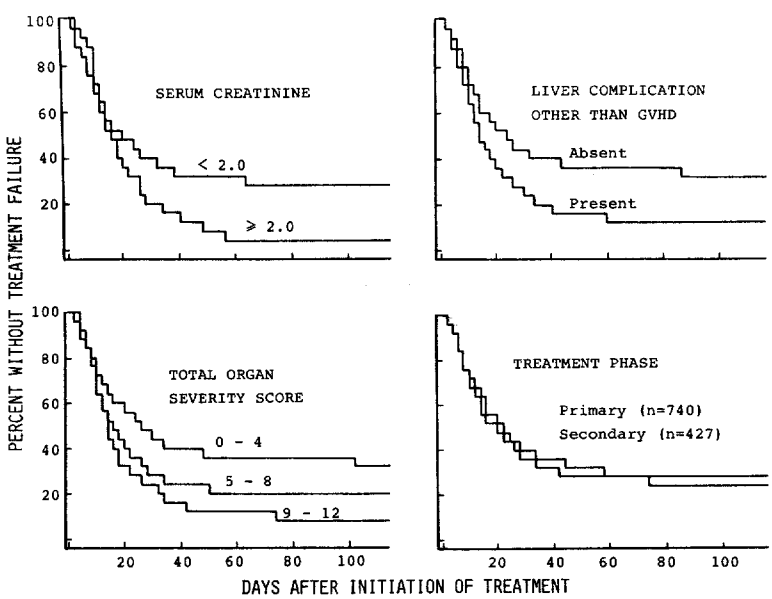

Fig 2. Association between risk factors and treatment failure. Survival plots indicate the proportion of patients alive and not requiring further treatment for acute GVHD. Deaths due to relapse are censored according to the method of Kaplan and Meier.[26]

represent the factors most reliably associated with outcome.[19] For primary therapy, the unfavorable factors that entered both types of models were single-agent prophylaxis, ATG treatment, HLA disparity, the presence of a liver complication other than GVHD, and early onset of GVHD, none of which appeared to represent major prognostic indicators of outcome after secondary treatment. For secondary therapy, the only such factor was the overall severity of skin, liver, and gut dysfunction at the start of secondary treatment. Overall pretreatment severity did not appear to represent a major prognostic indicator of outcome for primary therapy. Despite these differences for variables that entered both types of models, consistencies did appear in the models of time to treatment failure after primary and secondary therapy. The overall severity of skin, liver, and gut dysfunction at the beginning of each treatment cycle and the presence of a liver complication other than GVHD were associated with a higher likelihood of failure after both primary and secondary treatments. In particular, patients with hepatic complications other than GVHD had more severe liver dysfunction at the beginning of both primary and secondary treatment, and fewer had improvement in hepatic function after treatment. The association between the presence of a hepatic complication other than GVHD and decreased time to treatment failure may be partly explained by more rapidly rising serum bilirubin levels caused by more than one type of hepatic injury in this group of patients.

Increasing the dose of glucocorticoids appears to represent the most effective therapeutic strategy when GVHD recurs during the taper phase of primary treatment with glucocorticoids. However, less than half of the patients in this situation showed durable overall improvement, and results for other patients were less favorable. The proportion of patients receiving additional treatment was somewhat lower with secondary therapy than with primary therapy, possibly reflecting the higher nonrelapse mortality rate after secondary therapy. On the other hand, the times to treatment failure and the proportions of patients in various response categories were similar for primary and secondary treatment. These results suggest that the potential efficacy of new immunosuppressive agents can be assessed meaningfully in patients who have not responded adequately to primary treatment. Except for patients who have GVHD recurring during the taper phase of primary therapy with glucocorticoids, outcome after secondary therapy appeared to be influenced more by the severity of organ dysfunction in the skin, liver, and gut than by the agent(s) used for treatment. Studies attempting to evaluate the potential efficacy of new immunosuppressive agents in this setting should carefully account for the influence of disease severity at the beginning of treatment.

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