Predictors of Death From Chronic Graft-Versus-Host Disease After Bone Marrow Transplantation


Chronic graft-versus-host disease (chronic GVHD) is a frequent complication following allogeneic bone marrow transplantation (BMT), occurring in 30% to 45% of patients. The most commonly identified risk factors for the development of chronic GVHD have included the prior occurrence of acute GVHD, increasing patient age (especially among those with no or mild acute GVHD), and the use of viable buffy coat cells as part of the preparative regimen. Donor age and cytomegalovirus (CMV) infection have also been suggested as risk factors by some investigators, but these factors have not been confirmed to be predictive in other studies.

Less attention has been given to predictors of outcome among patients with chronic GVHD. Limited involvement of skin or liver only (“limited” chronic GVHD) has been associated with a good prognosis. The mode of presentation has been reported to be an important determinant: patients with progressive presentation (acute GVHD evolving into chronic GVHD without resolution of acute GVHD; hazard ratio of 4.1, 95% CI = 2.1 to 7.8), lichenoid changes on skin histology (hazard ratio of 2.2, 95% CI = 1.1 to 4.3), and elevation of serum bilirubin (>1.2 mg/dL (hazard ratio = 2.1, 95% CI = 1.1 to 4.1). Actuarial survival of 23 chronic GVHD patients with none of these risk factors was 70% at 6 years (95% CI = 38%, 88%). Thirty-eight patients with one of these risk factors had a projected 6-year survival of 43% (95% CI = 21%, 63%). The 29 patients with any combination of two or more of these factors had a projected 6-year survival of only 20% (95% CI = 8%, 37%). Identification of baseline risk factors should facilitate design of trials of chronic GVHD therapies and assignment of high-risk patients to more aggressive innovative therapeutic regimens.

METHODS

Patients

All patients receiving allogeneic BMT between November 1976 and June 1987 at The Johns Hopkins Oncology Center were followed until death or through December 17, 1987. All surviving patients were followed for a minimum of 250 days. Preparative regimens, GVHD prophylaxis, and supportive-care management strategies have been previously described. Patients were given oral trimethoprim-sulfamethoxazole twice daily from time of engraftment to 6 months after transplant and during immunosuppressive therapy for chronic GVHD.

Definitions

Acute and chronic GVHD were diagnosed using clinical and histologic criteria of skin and other affected tissues as previously described. The grading of acute GVHD was that described by Tutschka, et al and patients with overall clinical stage 1 or greater were considered to have acute GVHD (rash involving 30% or more of skin surface plus histologic changes of grade 2 or greater and/or systemic involvement). Patients with acute GVHD were classified as having cutaneous involvement only (stage 1) or systemic involvement (if liver or gastrointestinal [GI] tract also involved; stages 2 through 4 combined). Patients with chronic GVHD demonstrated both clinical and histologic evidence for chronic GVHD. The histology of chronic GVHD was characterized as lichenoid or sclerodermatous. Lichenoid chronic GVHD had features similar to idiopathic lichen planus: hyperkeratosis, hypergranulosis, irregular acanthosis, cytoplasmic vacuolization of the basal cell layer, dyskeratosis and colloid body formation, and a lymphocytic bandlike infiltrate in the papillary dermis in direct apposition to the epidermis. Sclerodermatous chronic GVHD was characterized by the presence of dermal sclerosis generally with loss of the distinction between the papillary and reticular dermis. The cutaneous appendages often appeared encased in collagen and tended to disappear. There usually was only a sparse perivascular or pericapillary infiltrate, and the overlying epidermis showed features similar to lichenoid chronic GVHD. Limited (limited cutaneous involvement only or hepatic dysfunction only) and extensive involvement were used as previously described. The modes of presentation were progressive (development after acute GVHD without remission from acute GVHD), quiescent (development after remission from...
acute GVHD), and de novo (without preceding acute GVHD), as previously described.17 Mucosal involvement was defined as clinical documentation of lichenoid oral mucositis with or without ulcers or pseudomembranous conjunctivitis.17 Exocrine involvement was defined as oral sicca symptoms or evidence of dry eyes on ophthalmic examination (abnormal tear production on Schirmer’s test and positive Rose bengal staining).17

Factors Assessed

Clinical and histologic parameters were assessed at the time of diagnosis of chronic GVHD before treatment was initiated. Factors assessed were age, prior occurrence of acute GVHD (classified as none [0], cutaneous involvement [1], or systemic involvement [2]); number of days after transplant; leukocyte count; platelet count; bilirubin; hepatic transaminases; alkaline phosphatase; serum immunoglobulin (IgG) expressed as a percent of the lower limits of normal for patient age (referred to as “normalized”); lichenoid cutaneous histologic pattern (compared to sclerodermatous); mode of presentation (progressive, quiescent, or de novo); oral or ophthalmic mucosal involvement; exocrine dysfunction of lacrimal or salivary glands; Karnofsky performance status score; limited or extensive involvement; prior CMV infection; pretransplant diagnosis; preparative therapy; gender; and donor/patient sex matching. Also evaluated was the extent of skin-surface involvement, graded as none (= 0), <25% of surface area (=1), 26% to 50% (=2), and >50% (=3).

Most patients received prednisone plus azathioprine as the therapy for chronic GVHD. Since treatment was not uniform in all patients and therapy was anticipated to influence outcome, patients were grouped according to treatment (prednisone plus azathioprine vs other treatments) to assess its effect on outcome when controlled for baseline prognostic factors. Since improvements in the management of infections have occurred over the years, the effect of year of transplant on survival was also assessed.

Statistical Methods

The major statistical endpoint of this study was survival following the onset of chronic GVHD. Survival distributions were estimated using the method of Kaplan and Meier and compared using the logrank statistic. For continuously distributed prognostic factors (eg, age), prognostic significance was assessed using the Cox proportional hazards model. This model was also used in a multivariate analysis to assess the prognostic significance of factors in the presence of other factors that influence survival. A second endpoint of interest was factors associated with the choice of prednisone and azathioprine therapy. To examine the influence of prognostic factors on the choice of prednisone plus azathioprine therapy, a logistic regression model was used.17

For the multivariate analyses, all variables found to be either statistically significantly or marginally prognostic (P < .15) or potentially strong predictors (hazard ratio > or = to 2.0) in univariate analyses were included in a multiple proportional hazards regression. Statistically nonsignificant effects were removed from the model in a stepwise fashion with re-estimation of parameters and significance levels at each step. Consequently the final model contained only prognostically strong or statistically significant effects. Because of the multiple statistical tests performed in the process of model building, the overall type I error rate for the multivariate models is >.05.

After building a final multivariate model for survival, a composite prognostic-factor score was calculated for each individual. This score was taken to be a weighted average of prognostic factor values with weights determined by the estimated coefficients from the proportional hazards model (ie, the score is simply the patient's hazard relative to the most favorable level of all prognostic factors). Patients were then grouped according to the value of their prognostic factors score. Survival curves for the resulting groups were then plotted. The statistical test of heterogeneity among survival curves produced in this fashion is equivalent to the overall test of significance for terms in the multivariate model.

RESULTS

Patient Characteristics

Eighty-five of 496 (17%) recipients of allogeneic BMT developed chronic GVHD. Table 1 gives the characteristics of the patients with chronic GVHD. Cyclosporine was given to 47 patients as GVHD prophylaxis, and cyclophosphamide or methotrexate was given to the remaining 38 as GVHD prophylaxis. Acute GVHD had not occurred earlier in 24; overall clinical stage 1 acute GVHD occurred in 40, and stages 2 through 4 acute GVHD had occurred in 21. Onset of chronic GVHD was a median of 126 days after BMT (range 30 to 713 days).

Baseline and Follow-up Characteristics

Baseline clinical and laboratory characteristics of the patients with chronic GVHD at the time of onset (before institution of treatment) are given in Table 2.

The actuarial survival after onset of chronic GVHD is depicted in Fig 1. Forty-four of the 85 patients (52%) were
still alive as of December 17, 1987. The projected 10-year survival was 42% (95% CI = 29%, 54%). Most deaths occurred within the first 2 years of GVHD onset, but deaths continued to occur up to 6 years after onset. Only four of the 41 deaths (10%) were due to relapse of the underlying malignancy for which the patient was transplanted. Of those still alive, follow-up was 251 to 3,934 days after transplant, with a median of 1,540 days; and 142 to 3,550 days after chronic GVHD onset, with a median of 1,340 days. Deaths occurred at a median of 207 days after onset of chronic GVHD (range of four to 2,100 days). Fifty-six patients (66%) received prednisone plus azathioprine for chronic GVHD. Other chronic GVHD treatments used were prednisone alone (13), prednisone plus cyclosporin (5), other (3), none (4), and not known (4) at time of analysis. The Karnofsky scores among survivors were 40% to 100%, with a median of 90%. Five patients had a score of less than 70%.

The actuarial survival according to mode to presentation is presented in Fig 2. Patients with de novo presentation had a projected 8-year survival of 53% (95% CI = 23%, 77%). Quiescent presentation was associated with a survival of 56% (95% CI = 36%, 72%). Patients with progressive presentation had a significantly lower survival of 10% (95% CI = 1%, 28%) than patients with de novo presentation (P < .001).

Predictors of Survival

Univariate analyses. Table 3 gives the hazard ratios, 95% confidence intervals (CI), and P values for the association of a variety of baseline factors with death. Significant risk factors for death were the prior occurrence of acute GVHD (either cutaneous or systemic), earlier onset time (of chronic GVHD) after transplant, low platelet count, elevated bilirubin, low serum IgG (as an absolute value and normalized), greater extent of skin involvement, lichenoid features in the skin histology, progressive presentation, and low Karnofsky scores. Predictive of survival was the de novo presentation mode and limited involvement. The year of transplant did not affect survival (hazard ratio = 1.045, P = .46).

Multivariate analysis. A stepwise Cox proportional-hazards model testing the factors identified in the univariate analyses was developed. The following baseline factors were tested: acute GVHD, onset day after transplant, platelet count, bilirubin, IgG, normalized IgG, skin extent, lichenoid skin histology, de novo and progressive presentations, Karnofsky score, and limited involvement. Three factors were independent predictors for death: abnormal bilirubin (>1.2 mg/dL), lichenoid skin histology, and progressive presentation (Table 4).

Twenty-three patients had none of these three risk factors: 18 (78%) were alive at the latest follow-up assessment. Of

| Leukopenia (leukocyte count ≤3,000/μL) | 14/84* | (17%) |
| Thrombocytopenia (platelets ≤100,000/μL) | 38/84 | (45%) |
| Hyperbilirubinemia (bilirubin >1.2 mg/dL) | 28/83 | (34%) |
| Elevated SGOT (>twice normal) | 34/83 | (41%) |
| Elevated SGPT (>twice normal) | 41/83 | (49%) |
| Elevated alkaline phosphatase (>twice normal) | 29/82 | (35%) |
| Decreased serum IgG (<325 mg/dL) | 20/77 | (26%) |
| Decrease in normalized IgG (≤0.5)† | 18/77 | (23%) |
| Limited involvement | 8/85 | (9%) |
| Skin extent involved (>50% body surface) | 25/81 | (31%) |
| Mucosal involvement | 50/70 | (71%) |
| Exocrine involvement | 32/78 | (41%) |
| Presentation: | | |
| De novo | 24/85 | (28%) |
| Progressive | 26/85 | (31%) |
| Quiescent | 35/85 | (41%) |
| Decreased Karnofsky performance status (<70%) | 33/83 | (40%) |

*Denominator indicates number of patients for which data was present.
†Expressed as a fraction of the age-adjusted lower limits of normal.
PREDICTORS OF DEATH FROM CHRONIC GVHD

Fig 2. Actuarial survival in years after chronic GVHD onset of patients grouped by mode of presentation (24 patients with de novo, 35 patients with quiescent, and 26 patients with progressive presentation). Survival of patients with progressive presentation was significantly less than that of patients with de novo presentation ($P < .001$), but survival of patients with de novo and quiescent presentations did not significantly differ ($P = .307$). The overall $P$ value (for heterogeneity) is $<.001$.

<table>
<thead>
<tr>
<th>Table 3. Prognostic Factors for Death in Patients With Chronic GVHD by Univariate Proportional Hazards Analyses</th>
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<tbody>
<tr>
<td>Factor*</td>
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<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Progressive presentation</td>
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<tr>
<td>Bilirubin†</td>
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<tr>
<td>Karnofsky score‡</td>
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<tr>
<td>Platelet count‡</td>
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<tr>
<td>IgG‡</td>
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<tr>
<td>Skin extent</td>
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<tr>
<td>Normalized IgG‡</td>
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Acute GVHD:
- Cutaneous
  - 3.038 | 1.293 - 7.134 | 0.011 |
- Systemic
  - 2.666 | 1.048 - 6.786 | 0.040 |
- De novo presentation
  - 0.377 | 0.167 - 0.852 | 0.019 |
- Lichenoid histology
  - 2.103 | 1.096 - 4.035 | 0.025 |
- Onset of CGVHD† | 0.996 | 0.983 - 1.000 | 0.035 |
- Limited involvement
  - 0.165 | 0.023 - 1.202 | 0.075 |
- Exocrine involvement
  - 0.668 | 0.346 - 1.290 | 0.229 |
- Cyclosporin prophylaxis
  - 1.403 | 0.739 - 2.663 | 0.301 |
- Alkaline phosphatase† | 1.001 | 0.999 - 1.001 | 0.308 |
- SGOT† | 0.999 | 0.996 - 1.001 | 0.368 |
- Transplant year† | 1.045 | 0.931 - 1.173 | 0.457 |
- Leukocyte count† | 0.977 | 0.988 - 1.006 | 0.522 |
- CMV shedding | 0.788 | 0.349 - 1.780 | 0.567 |
- SGPT† | 0.999 | 0.997 - 1.002 | 0.827 |
- Age† | 1.006 | 0.977 - 1.036 | 0.880 |
- Sex mismatch
  - 0.912 | 0.481 - 1.727 | 0.777 |
- Exocrine involvement
  - 1.064 | 0.558 - 2.029 | 0.850 |
- Sclerodermatous histology
  - 1.024 | 0.501 - 2.083 | 0.948 |
- Male gender | 1.015 | 0.531 - 1.938 | 0.965 |

*Types of pretransplant cytoreductive treatment and underlying diagnoses were not significantly associated with death. ($P$ values ranged between 0.42 and 0.99 for each preparative treatment or diagnosis compared with all others.)
†Incremental values.

The 33 patients with one risk factor, 19 (58%) were alive. Only six of the 22 patients (27%) with two risk factors present and only one of seven patients (14%) with all three risk factors were alive.

The effect of the presence of any combination of factors on a fatal outcome was examined by development of a prognostic factor score. The score for any given patient was derived by adding together the products of the coefficient (in Table 4) of each of the three factors (lichenoid skin histology, progressive presentation, abnormal bilirubin) times the value of the factor (0 if absent, 1 if present). Patients with none of the factors present (score of 0; 23 patients) had the best outcome, with an actuarial 6-year 70% survival (95% CI – 38%, 88%). Patients with scores greater than zero and up to 1.5 (presence of one of the risk factors; 33 patients) had a projected 6-year survival of 43% (95% CI – 21%, 63%). Patients with scores exceeding 1.5 (presence of at least two of the three prognostic factors; 29 patients) had only a 20% 6-year projected survival (95% – 8%, 37%). Figure 3 shows the actuarial survival of patients grouped by ranges of prognostic factor scores.

Effect of treatment on outcome. The same treatment (prednisone plus azathioprine) was used in two thirds of the patients. Because not all received the same therapy, we explored the possibilities that (1) the choice of treatment might have been influenced by the baseline factors, and (2) the effect of therapy on outcome may have been as important a determinant (or more so) than the baseline factors. Patients were grouped according to whether they received prednisone plus azathioprine (56 patients) or some other therapy (29 patients).

Table 5 shows that none of the baseline factors significantly predicted prednisone plus azathioprine as the initial choice of therapy. Thus there was no systematic bias of any of the baseline factors in the choice of therapy.

Furthermore, as shown in Fig 4, survival of the group of patients given prednisone plus azathioprine was no different...
than that of the group of patients given other therapies ($P < .30$). Thus, at least generally the type of therapy was less important a determinant of outcome in these patients than the baseline factors.

Because of a recent report describing the use of prednisone plus cyclosporine as therapy for high-risk chronic GVHD, this therapy was examined separately. Patients given prednisone plus cyclosporine ($N = 5$) all died, and this was significantly worse than survival of the 80 patients given other treatment ($P < .002$), as shown in Fig 5. This subgroup of patients all had at least two of the three adverse prognostic factors: all five had the progressive mode of presentation; four of the five had abnormal bilirubin; and four of the five had lichenoid skin histology. However, even accounting for the prognostic factors identified in the multivariate analysis of baseline factors, the choice of prednisone plus cyclosporine independently predicted a poor outcome ($P < .002$, Fig 5).

**DISCUSSION**

Chronic GVHD is a clinical syndrome with manifestations similar to those of collagen vascular disorders. Impaired in vitro responses to antigens, the presence of nonspecific suppressor cells, lymphoid hypocellularity of the thymic medulla and immaturity of splenic follicles, inability to reject third-party skin grafts, and the demonstration of autoreactive cytotoxic lymphocytes all are indicative of a profound immune dysregulation. Recurrent infection is a common complication and a frequent cause of death.

Previous studies have identified several baseline prognostic factors associated with adverse outcome from chronic GVHD. "Extensive" chronic GVHD (either multiorgan or extensive cutaneous involvement) has been noted to have a worse prognosis than "limited" involvement. Progressive presentation has been noted to carry a worse prognosis than quiescent or de novo presentation. Late onset has been said to be associated with a lower fatality. Thrombocytopenia has been noted to carry an adverse prognosis. Although the Karnofsky score of performance status has been noted to be a good indicator of the severity of chronic GVHD, it has not been evaluated as a baseline prognostic variable.

We identified a number of baseline factors predictive of death (in Table 3). Interestingly, although previous studies have noted age to be a risk factor for the occurrence of chronic GVHD, it was not prognostic for death from chronic GVHD. Oral and ophtalmic involvement (either mucosal or exocrine), which are frequent causes of morbidity from chronic GVHD, did not influence the risk of death. Prior CMV infection also did not affect the outcome.

Progressive presentation was the most important prognostic factor. This may simply reflect a greater magnitude of immune dysfunction in patients with concomitant, uncontrolled, acute GVHD and chronic GVHD, perhaps where both "alloimmune" and "autoimmune" cellular events are operative, interfering with normal immune function.

Elevated bilirubin was a significant risk factor, presumably as a marker for the degree of bile-duct damage. Early reports did not find any particular pattern of hepatic dysfunction in chronic GVHD to have a worse prognosis, and

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**Table 4. Prognostic Factors for Death in Patients With Chronic GVHD by Multivariate Proportional Hazards Analyses**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive presentation</td>
<td>1.400</td>
<td>4.054</td>
<td>2.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abnormal bilirubin*</td>
<td>0.7577</td>
<td>2.133</td>
<td>1.11</td>
<td>0.02</td>
</tr>
<tr>
<td>Lichenoid histology</td>
<td>0.7761</td>
<td>2.173</td>
<td>1.10</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* $> 1.2$ mg/dL.

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$^*$ From www.bloodjournal.org by guest on October 23, 2017. For personal use only.
quantification of abnormal liver function tests was not felt to be prognostic. Since hepatic tissue was not routinely obtained at onset of chronic GVHD for histologic evaluation, our data do not allow us to examine the prognostic role of specific hepatic histologic patterns.

Lichenoid (as opposed to sclerodermatous) chronic GVHD was also a poor prognostic factor. In some patients, lichenoid histologic features in the skin appear to be an earlier stage of chronic GVHD than the sclerodermatous form. Thus the absence of lichenoid changes could suggest spontaneous abatement of the disease activity and thus a more benign course. However, some patients have both lichenoid and sclerodermatous chronic GVHD either synchronously or metachronously. Thus, alternatively, lichenoid and sclerodermatous chronic GVHD may be qualitatively different immunopathologic processes that may coexist or be separate. Certainly the two histologic forms of cutaneous chronic GVHD appear to affect different target cells: epidermal cells are primarily affected in lichenoid chronic GVHD and fibroblasts in sclerodermatous chronic GVHD.

Based on the number of events in these patients, we estimate that this study can detect hazard ratios of approximately 1.6 as being statistically significant. Thus effects not observed to be significant may have modest prognostic importance. Also, the correlation of prognostic factors with one another causes only a few effects to be independently significant in multivariate models. Therefore factors excluded from multivariate models may be weak prognosticators or may be correlated with one or more factors in the model.

We did not find limited (compared with extensive) involvement or thrombocytopenia to be independent prognostic factors. Although in univariate analyses both appeared to carry prognostic value, other related factors appeared to carry more weight than these in multivariate analysis. Clearly patients with limited involvement had better survival than the overall group (six of seven patients compared to 45% of 78 patients with extensive involvement). The sole death in a patient with limited involvement was due to autopsy-documented idiopathic pulmonary fibrosis with progressive respiratory failure that began 1 to 2 years after the onset of chronic GVHD. Perhaps with larger numbers the difference in outcome for patients with limited versus extensive involvement may emerge as more important a prognostic variable than seen in this analysis.

Therapy with prednisone plus azathioprine was found to be associated with better survival in an uncontrolled retrospective analysis, but in a prospective, controlled study was
inferior to early treatment with prednisone alone in patients without thrombocytopenia. In thrombocytopenic patients, prednisone plus cyclosporin was superior to prednisone alone in sequential trials. However, even in “better” prognostic patients, despite 9 months of therapy, only 33% of patients given prednisone alone and only 37% of patients given prednisone plus azathioprine had complete resolution of active chronic GVHD; and in thrombocytopenic patients given prednisone plus cyclosporin, only 33% of patients had complete responses at 9 months. Exacerbation of chronic GVHD occurred in 10% to 14% of patients in complete remission when therapy was stopped. However, eventually therapy could be stopped in 81% of surviving patients. The inability of therapy to rapidly control chronic GVHD may explain why, at least in part, baseline factors were more important than treatment in predicting outcome in this analysis.

Of interest, all five patients given prednisone plus cyclosporin in this analysis died. These patients were all in a group with two or more adverse baseline prognostic factors. All had progressive presentation plus abnormal bilirubin and/or lichenoid histology. Sullivan et al. found that prednisone plus cyclosporin was superior to prednisone alone in thrombocytopenic patients in sequential nonrandomized trials. Although a small sample, the patients presented here had a less favorable outcome than seen in the patients in the report by Sullivan et al. There are several possible explanations for these seemingly disparate findings. The poor-prognosis patients treated with prednisone plus cyclosporin here may represent a “very high-risk” subset of Sullivan’s patients: only 16 of 44 (37%) thrombocytopenic patients in Sullivan’s report had progressive presentation. Indeed, in Sullivan’s analysis, 11 of 15 (73%) evaluable thrombocytopenic patients with progressive-onset chronic GVHD treated with prednisone plus cyclosporin died. Another possibility is that the type of acute GVHD prophylaxis influenced the type of effector cell in chronic GVHD. All of our patients were receiving cyclosporin when chronic GVHD occurred, and the effector cell generated in such patients may be different from that found in patients developing chronic GVHD who were not receiving any immunosuppressives or methotrexate.

Identification of baseline factors that carry different risks for death will assist in the evaluation of therapies of chronic GVHD by allowing stratified assignment to treatment groups. Additionally, use of these risk factors to identify patients likely to fail conventional therapy will permit earlier application of more aggressive or investigative therapies, such as thalidomide.

ACKNOWLEDGMENT

We are appreciative of the helpful comments of H. Joachim Deeg, MD.

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Predictors of death from chronic graft-versus-host disease after bone marrow transplantation

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