Increasingly Frequent Diagnosis of Acute Gastrointestinal Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

The reported incidence of grades II to IV acute graft-versus-host disease (GVHD) after hematopoietic cell transplantation with HLA-identical sibling donors has increased considerably during the past 15 to 20 years at our center. The purpose of this study was to evaluate the potential reasons for this change. We reviewed organ stages and overall grades of GVHD for 2220 patients who received a first marrow or peripheral blood cell transplant from an HLA-identical sibling or an HLA-allele-matched unrelated donor with the use of a posttransplantation immunosuppressive regimen that included both methotrexate and cyclosporine between 1985 and 2001. The most striking change was an increased incidence of stage 1 gut involvement from 10% to 20% before 1992 to 50% to 60% since 1992, both with related and unrelated donors. This change increased the incidence of grade II GVHD with sibling donors, such that the overall incidence of grade II to IV GVHD is now 60% to 70%. Among patients with chronic myeloid leukemia in chronic phase, the increasingly frequent diagnosis of acute GVHD since 1992 has not been associated with decreased survival. A high diagnostic sensitivity and increased awareness that gut GVHD can occur without skin involvement account for the increased incidence of acute GVHD at our center.

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KEY WORDS

Graft-versus-host disease  ●  Hematopoietic cell transplantation  ●  HLA-identical sibling donor  ●  Gastrointestinal

INTRODUCTION

Despite more than 30 years of experience with allogeneic hematopoietic cell transplantation (HCT), the assessment of acute graft-versus-host disease (GVHD) still poses a difficult challenge. Grading of GVHD can serve a variety of purposes, including retrospective assessment of peak severity, real-time evaluation of severity at prespecified intervals, determination of the need for treatment, prognostication for survival, and evaluation of new methods to prevent GVHD in prospective studies. The original criteria for grading GVHD were formally proposed in 1974 [1], and at least 2 modifications or refinements have been suggested and widely adopted since then [2,3]. One such modification was the agreement at a consensus conference that persistent nausea with histologic evidence of GVHD but no diarrhea should be included as stage 1 gut involvement [2]. It was also recommended that the nominal severity of liver or gut GVHD should be decreased by 1 stage when the organ was simultaneously affected by other complications, such as regimen-related toxicity or infection. A further refinement evolved from a registry study that suggested that correlations between peak GVHD grade and transplant-related mortality could be improved by assigning higher weight to the skin stage in computing the overall grade [3].

The assessment of GVHD severity necessarily involves some level of subjective judgment both at the
bedside and in the interpretation of medical records. We have previously questioned the reproducibility of retrospective GVHD grading and have suggested 2 different approaches for possible improvement, although neither approach has been demonstrably accepted or endorsed in any center [4,5]. Our awareness of the need for more robust methods of GVHD grading originated soon after 1991, when the task of assigning final GVHD grades at our center passed from 1 reviewer to another. This change was accompanied by an increase in overall GVHD grades, particularly after HCT with HLA-identical sibling donors. Moreover, the incidence rates of acute GVHD reported for patients who have had allogeneic HCT at our center remain considerably higher than those observed elsewhere, even when the same treatment protocols have been used. The purpose of this study was to evaluate potential reasons for the changes in GVHD incidence across 17 years at our center.

PATIENTS AND METHODS

Study Population

This study included patients who received their first marrow or peripheral blood cell transplants from HLA-identical siblings (n = 1754) or HLA-matched unrelated donors (n = 366) with the use of conventional pretransplantation conditioning regimens and a posttransplantation immunosuppressive regimen that included both methotrexate and cyclosporine [6-9]. Cases were excluded if complete GVHD grades were not available. HLA typing was performed with the use of serologic methods and DNA-based methods as previously described [10]. Unrelated donor/recipient pairs included in this study were identical for HLA-A, -B, -C, -DRB1, and -DQB1 alleles. Institutional review board approval was obtained to permit review of a database containing health information for identifiable subjects in this study. Characteristics of the study population are summarized in Table 1.

Transplantation Protocols

Transplantation protocols have been previously described [6,7,11-13]. Conditioning regimens typically included the use of high-dose cyclophosphamide together with fractionated total body irradiation (TBI) or high-dose busulfan. Trimethoprim and sulfamethoxazole were given for prevention of *Pneumocystis carinii* pneumonia. Laminar airflow rooms and oral nonabsorbable antibiotics were used for some patients until 1994. For patients in conventional hospital rooms, systemic antibiotics were administered to prevent bacterial infection when absolute neutrophil counts were less than 0.5 × 10^9/L. Acyclovir was administered to prevent herpes simplex virus reactivation in all seropositive recipients and was used before 1990 to prevent cytomegalovirus (CMV) reactivation in some seropositive recipients. Ganciclovir was administered either at the time of initial engraftment or preemptively at the first evidence of infection to prevent CMV disease in some CMV-seropositive patients beginning in 1990 and in all such patients beginning in 1991 [14,15]. Fluconazole was administered to prevent fungal infection for some patients beginning in 1990 and for all patients beginning in 1992 [16,17]. Intravenous immunoglobulin was administered to some patients in randomized prospective trials from

<table>
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<tr>
<th>Table 1. Characteristics of the Study Population</th>
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<tr>
<td>Diagnosis, n (%)</td>
</tr>
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<td>Acute lymphoblastic leukemia</td>
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<td>Acute myeloid leukemia</td>
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<td>Chronic myeloid leukemia</td>
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<tr>
<td>Myelodysplastic syndrome</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>Hodgkin disease</td>
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<td>Myeloma</td>
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<tr>
<td>Other</td>
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<td>Median age, y (range)</td>
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<td>Donor/recipient sex, n (%)</td>
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<tr>
<td>Mobilized peripheral blood cells</td>
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<td>Marrow and peripheral blood cells</td>
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GVHD Grading

GVHD grades were assigned for all patients, regardless of survival after the transplantation. Only 76 (3.4%) of the 2220 patients in this study died before day 21. In assigning GVHD grades, reviewers used research files containing copies of medical summaries written by primary providers every month, biopsy reports, correspondence with referring physicians, and autopsy reports. Biopsies were performed for diagnostic evaluation only in patients with symptoms. Medical summaries included paragraphs specifically describing the use of medications for prophylaxis and treatment of GVHD and discussions of any clinical manifestations of GVHD. Until 2000, the research charts included daily flow sheets of information abstracted from the original medical records. These flow sheets summarized the percentages of body surface involved with rash and the volumes of diarrhea. Beginning in 2000, flow sheets were replaced by summary information describing the maximum extent of body surface involved by rash and the maximum stool volume after day 21. Flow sheets and summary information both provided total serum bilirubin concentrations across time and indicated the presence of abdominal pain or blood in stools, the presence of gut or liver complications other than GVHD, biopsy results, and administration of immunosuppressive medications.

Reviewers followed patterns from the original Seattle criteria in assigning GVHD grades [1]. Information from biopsies was used to confirm the diagnosis of GVHD but was not used in the assignment of GVHD grades. J.E.S. was responsible for assigning GVHD grades until P.J.M. assumed this task in 1991. J.E.S. used clinical expertise in accounting for complications other than GVHD in assigning the severity of organ involvement, whereas P.J.M. adjusted organ stages according to the convention endorsed by a consensus conference in 1994 [2]. Briefly summarized, grade 0 indicates the absence of clinical manifestations of GVHD. Grade I GVHD indicates stage 1 or 2 skin involvement (<50% of body surface involved). Grade II GVHD indicates stage 3 skin involvement (>50% rash) or adjusted stage 1 liver (bilirubin 2–3 mg/dL) or gut (diarrhea with stool volume <1000 mL/d) involvement. Beginning in 1992, isolated upper gastrointestinal GVHD without diarrhea or rash was categorized as stage 1 gut involvement and grade II GVHD overall [2]. Grade III GVHD indicates stage 4 skin involvement (bullae) or adjusted stage 2 to 4 liver (bilirubin >3.0 mg/dL) or gut (stool volume >1000 mL/d) involvement, without GVHD as a major contributory cause of death. Grade IV GVHD indicates that GVHD was a major contributory cause of death.

RESULTS

Incidence of Overall GVHD Grades and Organ Stages across Time

The reported incidence rates of grade II to IV GVHD after HCT with HLA-identical sibling donors increased from 25% to 45% between 1985 and 1990 to 60% to 75% after 1990 (Figure 1). Although there were some changes from year to year, the incidence of grade III and IV GVHD did not show a consistent trend across time, suggesting that the major change across time was an increase in the incidence of grade II GVHD. In comparison to the dramatically increased incidence of grade II to IV GVHD with HLA-identical sibling donors across time, the incidence of grade II to IV GVHD with HLA-matched unrelated donors showed only modest increases across time, with no consistent changes in the incidence of grade III and IV GVHD.

We examined GVHD stages in the skin, liver, and gut to identify whether any individual organ accounted for the increased incidence of grade II to IV GVHD after HCT with HLA-identical sibling donors. The incidence of stage 1 gut involvement increased strikingly from 10% to 20% between 1985 and 1991 to 40% to 55% after 1991, whereas the incidence of stage 2 to 4 gut involvement did not show a consistent trend across time (Figure 2). A similarly striking increase in the incidence of stage 1 gut involvement also occurred with HLA-matched unrelated donors, whereas the incidence of stage 2 to 4 gut involvement seemed to decrease slightly. The distribution of GVHD stages in the skin and liver showed
no consistent trends across time with either related or unrelated donors (data not shown).

Incidence of Gastrointestinal Biopsy and Patterns of GVHD Manifestations among Patients with Grade II GVHD and Stage 1 Gut Involvement

From 1985 to 1991, approximately 20% to 30% of all patients had endoscopic or rectal biopsy for diagnostic evaluation of gastrointestinal complications during the first 100 days after HCT (Figure 3). Since 1992, the incidence of endoscopic or rectal biopsy has increased gradually to 50% to 60%. The increased use of endoscopic or rectal biopsy could have facilitated the diagnosis of gastrointestinal GVHD in the absence of cutaneous involvement. To test this hypothesis, we separated patients who had stage 1 gut involvement with or without stage 1 liver involvement but no skin involvement from those who had any other pattern of grade II GVHD. Results in Figure 4 show an increase in the incidence of stage 1 gut involvement without skin involvement after HCT with HLA-identical sibling donors, beginning in 1992. The results also suggest a more gradual increase in the incidence of other patterns of grade II GVHD in this group.

We reviewed biopsy and treatment records of all 168 patients with stage 1 gut involvement and no skin involvement after HCT from HLA-identical siblings to confirm the diagnosis. All but 7 (4%) had a gastrointestinal biopsy, and all but 2 (1%) received treatment for GVHD. All had either biopsy or treatment for gastrointestinal GVHD. In addition, case records were reviewed to assess symptoms reported for patients who had stage 1 gut involvement without skin GVHD during 2000 or 2001. Among 44 such cases, 18 (41%) had upper gastrointestinal symptoms without diarrhea, whereas the remainder had diarrhea with or without upper gastrointestinal symptoms.

We found a less striking increase in the incidence of stage 1 gut involvement without skin involvement after HCT from HLA-matched unrelated donors (Figure 4), whereas the incidence of other patterns of grade II GVHD showed no consistent trend across time. The incidence rates of stage 1 to 4 and 3 to 4 skin involvement were substantially higher with HLA-matched unrelated donors than with HLA-identical sibling donors (Figure 5). From 1992 to 2001, 86% of patients with stage 1 gut involvement after HCT with HLA-matched unrelated donors also had skin involvement, compared with 58% among patients with stage 1 gut involvement after HCT with HLA-matched sibling donors.

Use of Parenteral Nutrition

An increase in the true incidence of gastrointestinal GVHD across time should have caused increased used of parenteral nutrition after recovery from the
effects of the conditioning regimen. Contrary to this expectation, the proportion of patients who received parenteral nutrition beyond 3 weeks from the transplantation decreased across time (Figure 6). Until 1992, more than 90% of patients with HLA-identical sibling donors required parenteral nutrition at some time after day 21, and until 1993, the same was true for more than 98% of patients with HLA-matched unrelated donors. Since then, the incidence of parenteral nutrition after day 21 has decreased to approximately 66% with HLA-identical sibling donors and to approximately 75% with HLA-matched unrelated donors.

Correlation between GVHD Grade and Survival among Patients with Chronic Myeloid Leukemia in Chronic Phase

Because previous studies have used a correlation between the peak severity of acute GVHD and transplant-related mortality to demonstrate the validity and medical significance of different GVHD grades [1,20,21], it was of interest to determine whether the increasingly frequent diagnosis of GVHD since 1992 was associated with any change in transplant-related mortality. For this purpose, we selected patients with chronic myeloid leukemia (CML) in chronic phase at the time of the transplantation. These patients are particularly well suited for this analysis, because the risks of transplant-related mortality from causes unrelated to GVHD and the risks of recurrent malignancy and death after the development of recurrent malignancy are all low, thereby minimizing the confounding effect of complications other than GVHD.

Table 2 shows the distribution of GVHD grades for patients with CML in chronic phase who received HCT from HLA-matched unrelated donors from 1985 to 1991 was too small for meaningful analysis (n = 35). The last column of Table 2 shows the distribution of GVHD grades for patients with CML in chronic phase who received HCT from HLA-matched unrelated donors from 1992 to 2001. This cohort had a substantially higher incidence of grade III GVHD, with corresponding reductions in the incidence of grade 0 and I GVHD as compared with the 1992 to 2001 cohort of patients with HLA-identical sibling donors.

Within each cohort, the 1-year survival among patients with grade 0, I, or II GVHD showed no significant differences (Table 3). In the 1985 to 1991 cohort, 1-year survival for patients with grade III GVHD was not significantly lower than for those with grade 0 to II GVHD. In both 1992 to 2001 cohorts, however, 1-year survival for patients with grade III GVHD was lower than for those with grade 0 to II GVHD (P = .005 for sibling recipients and .007 for unrelated recipients; Wald test). All patients with grade IV GVHD died within 1 year after transplantation. The change in distribution between grade 0 and grade II GVHD among patients with HLA-identical sibling donors in the 1992 to 2001 cohort compared with the 1985 to 1991 cohort was not associated with a decrease in survival. In fact, 94% (95% confidence interval [CI], 90%-97%) of patients with grade 0 to II GVHD survived for 1 year in the 1992 to 2001

Table 2. Distribution of GVHD Grades after HCT among Patients with Chronic Myeloid Leukemia in Chronic Phase

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<tr>
<td>0</td>
<td>113 (48)*</td>
<td>70 (27)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>I</td>
<td>34 (14)</td>
<td>28 (11)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>II</td>
<td>58 (24)</td>
<td>133 (52)</td>
<td>81 (53)</td>
</tr>
<tr>
<td>III</td>
<td>28 (12)</td>
<td>20 (8)</td>
<td>45 (29)</td>
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<tr>
<td>IV</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td>3 (2)</td>
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*Data indicate the numbers (percentages) of patients in each category.

Table 3. One-Year Survival among Patients with Chronic Myeloid Leukemia in Chronic Phase, According to GVHD Grade

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<tr>
<td>0</td>
<td>89 (84-95)*</td>
<td>88 (81-96)</td>
<td>75 (84-95)</td>
</tr>
<tr>
<td>I</td>
<td>88 (77-99)**</td>
<td>96 (89-99)**</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>79 (68-90)**</td>
<td>96 (93-99)**</td>
<td>89 (82-96)</td>
</tr>
<tr>
<td>III</td>
<td>76 (62-91)**</td>
<td>65 (46-85)</td>
<td>67 (53-80)</td>
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<tr>
<td>IV</td>
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*Data indicate percentage (95% confidence interval) life-table survival at 1 year after the transplantation.

†The calculated upper limit of the 95% confidence interval exceeded 100%.
cohort, compared with 86% (95% CI, 82%-91%) in the 1985 to 1991 cohort (P = .01; Wald test).

In the 1992 to 2001 cohort, 1-year survival for sibling recipients who had CML in chronic phase and grade II GVHD with stage 1 gut involvement but no skin involvement was 98% (95% CI, 95%-99%), compared with 94% (95% CI, 88%-99%) for those with grade II GVHD and skin involvement (P = .18; Wald test). These results demonstrate that the presence or absence of skin involvement did not have a statistically significant effect on survival among patients with grade II GVHD.

**DISCUSSION**

Our current results indicate that approximately 60% to 70% of patients at our center experience grade II to IV acute GVHD after HCT from HLA-identical sibling donors. Approximately 30% of these patients, or 20% of the total, have stage 1 gastrointestinal symptoms in the absence of skin involvement. The original Seattle criteria for staging gut involvement included the assessment of diarrhea, nausea, and vomiting, each evaluated according to a 4-point scale of severity [1]. In theory, the overall severity of gut involvement was assigned to reflect the most severe symptom, but in practice, the staging of gut involvement was limited to the assessment of stool volume because of the difficulty in applying quantitative scales for assessment of nausea and vomiting. In fact, the minimum stool volume proposed in 1974 as indicative of intestinal GVHD (500 mL/d) greatly exceeds the normal upper limit (200 mL/d) in someone who is eating and represents florid secretory diarrhea in someone who is fasting. Results of a prospective study have shown that GVHD is the most common cause of diarrhea after HCT, even when stool volumes do not reach the 1974 threshold [22].

Resurgent clinical appreciation of upper gastrointestinal symptoms as a manifestation of GVHD came primarily from 3 studies. In 1986, Spencer et al [23] reported a prospective study of 50 patients who were evaluated for unexplained nausea and vomiting. GVHD was identified as the sole cause of symptoms in 13 cases and a contributory cause together with infection in 8 cases. Skin GVHD was present in 16 of the 21 cases, but stool volume exceeded 500 mL/day in only 2 cases. In 1990, Weisdorf et al [24] reported a retrospective review in which upper gastrointestinal symptoms were identified in 62 of 469 cases of GVHD. In this series, the presentation of upper gastrointestinal symptoms was always accompanied by GVHD in other organs. In 25 cases, upper gastrointestinal GVHD presented with rash involving <50% of the body surface as the only other manifestation of GVHD. In 1998, Wu et al [25] reported a prospective study of 76 patients who had 78 episodes of persistent nausea and anorexia after marrow transplantation. GVHD was identified as the sole cause of symptoms in 63 cases (81%). It is important to note that 39 of the 63 cases had no other manifestations of GVHD, similar to findings in our study.

The findings of the present study could be explained by a true increase in the incidence of GVHD or by an increase in sensitivity for making the diagnosis across time. For this reason, we have carefully considered changes in population characteristics and treatment as possible explanations for a change in the incidence of GVHD. Characteristics of the 1985 to 1991 and 1992 to 2001 cohorts of patients with HLA-identical siblings donors differed in patient age, the use of TBI in the conditioning regimen, and the source of cells used for the transplant. Patients in the 1992 to 2001 cohort were older than those in the 1985 to 1991 cohort, but multivariate analysis showed that this difference did not account for the higher incidence of GVHD in the 1992 to 2001 cohort (data not shown). The decreased use of TBI in the 1992 to 2001 cohort is not likely to account for the increased incidence of GVHD, because higher-dose TBI regimens have been associated with an increased incidence of GVHD [21]. Finally, results of randomized trials have shown that the incidence of acute GVHD is at most only slightly increased by the use of mobilized blood as opposed to marrow [26,27]. Hence, the differences between the 1985 to 1991 and 1992 to 2001 cohorts are not likely to account for the increased incidence of GVHD across time.

During the early 1990s, 3 major changes in clinical practice that could have affected the incidence of GVHD were made at our center. The use of laminar airflow isolation was abandoned, the use of ganciclovir for preemptive treatment of CMV infection was begun, and prophylactic administration of fluconazole throughout the first 75 days after the transplant was introduced. Randomized clinical trials showed that laminar airflow isolation reduced the incidence of acute GVHD among patients with aplastic anemia [20] but not among patients with hematological malignancies [28], in whom effective gut decontamination is difficult to achieve [29]. Similarly, a prospective study of ganciclovir administered at the time of engraftment in CMV-seropositive recipients showed no significant effect on the incidence of grades II to IV GVHD [14]. A randomized prospective study of prophylactic fluconazole administration showed no significant effect on the incidence of grades II to IV GVHD, on the overall distribution of gut stages or on the incidence of stages 1 to 4 or 2 to 4 gut involvement [17]. The results of these studies suggest that practice changes introduced during the early 1990s cannot account for the increased incidence of gut GVHD across time at our center.
The advent of preemptive therapy for CMV infection has virtually eliminated CMV enteritis as a cause of gastrointestinal symptoms in our center, and most patients with anorexia, nausea, vomiting, or diarrhea persisting beyond day 20 after allogeneic HCT are now diagnosed with acute GVHD [22,25,30-32]. In nearly all cases, the diagnosis is supported by gastric [33], or less often rectal, biopsy, made available through the services of full-time gastroenterology consultants dedicated to the management of HCT recipients. It is conceivable that gut GVHD has been overdiagnosed in our center since 1992, but the diagnosis was confirmed by biopsy in nearly all cases. Other explanations for nausea, vomiting, and diarrhea were generally not apparent when GVHD was diagnosed, and gastrointestinal symptoms attributed to GVHD have typically resolved after starting glucocorticoid treatment [25]. Given the absence of other explanations for changes in the incidence of GVHD, we believe that isolated gut GVHD was undiagnosed in our center before 1991. Reassessment of these cases is not possible because gastroenterology consultation was not routinely requested for patients who had upper gastrointestinal symptoms without diarrhea, and biopsy confirmation of the diagnosis is not available.

The experience of our pathologists in reviewing outside specimens has suggested that gastrointestinal GVHD was also underdiagnosed in other centers during the 1980s. The diagnostic sensitivity of histopathology has improved since then, but practices still vary considerably with respect to the frequency of gastroenterology consultation, the use of endoscopy, the sites selected for biopsy, the number of biopsies taken, the processing of samples, and the number of sections reviewed [33].

Our data suggest that early diagnosis and appropriate treatment of upper gastrointestinal GVHD can decrease morbidity, although treatment does not affect survival because mortality associated with upper gastrointestinal GVHD is low. We hypothesize that earlier diagnosis and treatment of gastrointestinal GVHD explains the decreased administration of parenteral nutrition after day 21, although improvements in control of CMV infection during the past decade could also have contributed to this effect. The increased incidence of acute GVHD across time in our center and the strikingly different incidence rates of acute GVHD among centers ostensibly using closely similar approaches for prophylaxis highlight the need for considerable caution in the interpretation of published GVHD incidence data. Until more robust methods for grading acute GVHD are developed, we would favor the use of double-blind designs, whenever feasible, for future prospective phase III studies in which the incidence of acute GVHD is the primary outcome of interest.

ACKNOWLEDGMENTS

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