Acute Graft-Versus-Host Disease: Grade and Outcome in Patients With Chronic Myelogenous Leukemia


Acute graft-versus-host disease (aGVHD) has been classified according to the Seattle criteria as grades 0, I, II, III, and IV for 20 years. The predictive value of such detailed grading is a matter of debate; publications usually report GVHD as present or absent or as absent, moderate, or severe. The Working Party Chronic Leukemia of the European Group for Bone Marrow Transplantation analyzed data of 1,294 patients transplanted from an allogeneic donor for chronic myelogenous leukemia (CML) in first chronic phase and tested the predictive value of aGVHD grading for the following endpoints: day 100 mortality (D100M), transplant-related mortality (TRM), relapse incidence (RI), leukemia-free survival (LFS), and survival (SURV). aGVHD was absent in 462 patients (35.7%), grade I occurred in 335 (25.8%), grade II in 264 (20.5%), grade III in 110 (8.5%), and grade IV in 123 patients (9.5%). A total of 297 patients (23%) died within 100 days, 485 patients (38%) died of any TRM, and 100 patients (8%) died of relapse. D100M according to grades 0, I, II, III, and IV was 17%, 13%, 19%, 38%, and 70%, respectively, with significant difference between 0-II versus III-IV. TRM was 28%, 27%, 43%, 68%, and 92%, respectively, with a distinct separation between 0-I versus II-IV. RI showed a continuous decrease of 37%, 30%, 23%, 18%, and 8%, respectively, with increasing aGVHD. LFS was 45%, 51%, 44%, 26%, and 7%, respectively, and was best for patients with grade I aGVHD. This finding was also reflected in a better overall survival (60%, 64%, 53%, 30%, and 8%, respectively). The better LFS for grade I aGVHD patients compared with patients with grade 0 or II aGVHD was confirmed (P = .05) in a multivariate analysis. These data document the value of the present 5-point grading of aGVHD, ie, different outcome is observed depending on endpoint analyzed. Restricting information about aGVHD to presence or absence is not warranted.

Graft-Versus-Host disease (GVHD) remains a major complication of allogeneic bone marrow transplantation (BMT) and a significant determinant for outcome.7,8 Acute GVHD (aGVHD) is traditionally classified according to the Seattle criteria in a 5-point clinical staging system according to the three main organs involved: skin, gastrointestinal tract, and liver.1 Based on these organ scores, an overall clinical grading was defined from 0 to IV. The value of such a finely tuned classification system as a predictive tool has never been analyzed in detail. In some analyses, patients with overall grades 0 and I are considered as “aGVHD absent” and patients with grades II, III, and IV as “aGVHD present.”8 Alternatively, aGVHD is reported as absent (grade 0), mild or moderate (grades I and II), or severe (grades III and IV).

Using a large cohort of patients treated with allogeneic BMT for one indication, chronic myelogenous leukemia (CML) in first chronic phase, we examined the influence and prognostic value of this 5-point overall grading system of aGVHD. Our study was initiated by a workshop held at an UCLA conference on bone marrow transplantation (January 1994, Keystone, CO) and intended as a review of the 25 years of experience with the Seattle criteria that addressed the prognostic value of the 5-point grading on the following endpoints: day 100 mortality (D100M), transplant-related mortality (TRM), relapse incidence (RI), leukemia-free survival (LFS), and overall survival (SURV). In addition, the conventional 5-point scale was compared with a dichotomized system using absence or presence of GVHD and a system using absent, moderate, or severe as grading.

PATIENTS AND METHODS

Study design and data collection. The present analysis is a retrospective study based on data collected by the EBMT between 1979 and 1990. The data were collected by questionnaire containing information on donor and recipient identity, sex, age, and histocompatibility. Moreover, patient data were available on primary disease, transplant procedure, conditioning, GVHD prevention method, and outcome.

The data were collected annually and updated as of January 1, 1993. For logistic reasons, not all teams reported all their patients. Some teams ceased to report, whereas some only began reporting at a later stage. The participating institutions are listed in the Appendix.

Patients. The present analysis concentrates on 1,294 patients with CML transplanted in first chronic phase of their disease with bone marrow from an allogeneic donor. Identical twin transplants and patients with second transplants were excluded.

Table 1 summarizes the patient and transplant characteristics in regard to age, donor recipient sex combination, GVHD prevention method, donor source, year of transplant, and interval from diagnosis to transplant. Of the 1,294 patients with CML, 58% were male and 42% were female. Male patients receiving female bone marrow represent 330 cases (26%). The median age was 33 years, with a range from 0.5 to 58 years. One hundred fifty-two patients (12%) were 20 years or younger and 1,142 patients were older than 20 years.

The donor was an HLA-identical sibling in 90% of the patients (n = 1,160) and a nonidentical related or unrelated donor in 10% (n = 134). For 30% of all patients (n = 385), donor marrow was T-cell depleted as method of GVHD prevention. Fifty-five percent of transplants were performed before 1988 and 45% between 1988 and 1990. The interval from diagnosis to transplant was ≤1 year in

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Table 1. Incidence and Severity of aGVHD Depending on Age, Sex, T-Cell Depletion, Donor Source, Year of Transplant, and Interval From Diagnosis to Transplant for 1,294 CML Patients With an Allogeneic BMT in First Chronic Phase

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>No. of Patients (%)</th>
<th>Grade of aGVHD (%)</th>
<th>Incidence (0 v I-IV)</th>
<th>Severity (0 to IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,294 (100)</td>
<td>35.7</td>
<td>25.8</td>
<td>20.5</td>
</tr>
<tr>
<td>Age of patient (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>152 (12)</td>
<td>42</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1,142 (88)</td>
<td>35</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Donor recipient sex combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female donor/male recipient</td>
<td>330 (26)</td>
<td>37</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>964 (74)</td>
<td>35</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>GVHD prevention method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No T-cell depletion</td>
<td>809 (70)</td>
<td>29</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>T-cell depletion</td>
<td>385 (30)</td>
<td>51</td>
<td>26</td>
<td>14</td>
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<td>Donor source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-identical sibling</td>
<td>1,160 (90)</td>
<td>37</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Nonidentical related donor</td>
<td>44 (3)</td>
<td>32</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>90 (7)</td>
<td>21</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Year of BMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1987</td>
<td>718 (55)</td>
<td>38</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>≥1988</td>
<td>576 (45)</td>
<td>32</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>Interval between diagnosis and therapy (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td>592 (47)</td>
<td>39</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>13-24</td>
<td>352 (28)</td>
<td>28</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>≥24</td>
<td>322 (26)</td>
<td>35</td>
<td>25</td>
<td>22</td>
</tr>
</tbody>
</table>

* χ² test.  
† Mann-Whitney test.  
‡ Kruskall-Wallis test.

RESULTS

Follow-up and endpoints. At the time of analysis, 699 of 1,294 patients (54%) were alive, 563 (44%) were alive without relapse at time of last follow-up, and 595 had died (46%). Median follow-up of living patients was 52 months.

Two hundred ninety patients (23%) died within 100 days of transplant; 15 patients were censored within 100 days. A total of 495 patients (38%) died of TRM and 236 patients (18%) relapsed, 100 (8%) of whom died.

Incidence and severity of aGVHD. Although 462 patients (36%) never had any signs of aGVHD, 832 patients (64%) showed grades I to IV; 497 (38%) had grade II or higher aGVHD. The individual grades are listed according to age, sex, GVHD prevention method, donor source, and year of BMT (Table 1). Incidence and severity were similar in the two sex-matched categories and two age classes. There were large and significant differences in incidence and severity of the aGVHD grades for GVHD prevention and donor source. Patients with T-cell-depleted bone marrow had less GVHD and patients with donors other than HLA-identical siblings had more frequent and more severe aGVHD. There was no difference in severity of GVHD in the two time cohorts, but a slightly larger number of patients transplanted before 1988 had no GVHD. This coincides with the time period of more T-cell depletion.

Influence of acute GVHD on D100M, TRM, RI, LFS, and SURV. The presence and severity of aGVHD have a strong impact on D100M, TRM, RI, LFS, and SURV (Fig 1 and Table 2). Patients with no GVHD have lower D100M and TRM but higher RI than do patients with GVHD. There is an increase in D100M and TRM with increasing aGVHD.

47%, between 1 and 2 years in 27%, and more than 2 years in 26% of the patients.

Grading of aGVHD and endpoints. The participating teams were asked to enter the grade of aGVHD according to the Seattle criteria. To investigate the influence of the aGVHD grade, we looked at several endpoints: D100M, TRM, RI, LFS, and SURV. The criteria defining these endpoints have been published. For each of the grades I or higher, relative risks with respect to grade 0 were assessed. Adjustments for other covariables were made for the covariables sex match, age, donor source, T-cell depletion, year of BMT, and interval from diagnosis to transplant by the Kruskall-Wallis test.

Statistical analysis. Discrete variables in cross-tables and incidence of aGVHD (grade 0 v I + II + III + IV) in Table 1 was analyzed with the χ² test. Severity was compared for the different categories of age, sex, GVHD prevention method, and year of BMT by the nonparametric Mann-Whitney test and for the donor source and interval from diagnosis to transplant by the Kruskall-Wallis test. The influence of different grades of aGVHD on D100M was analyzed with a logistic regression. For each of the grades I or higher, relative risks with respect to grade 0 were assessed. Adjustments are made for the covariables sex match, age, donor source, T-cell depletion, year of BMT, and interval from diagnosis to transplant, as listed in Table 1. Similar analyses were performed for the other endpoints using Cox regression. To assess the influence of moderate aGVHD on relapse and LFS, the same analyses were repeated but limited to the 1,061 patients with grade 0, I, or II aGVHD. Relapse incidence was also compared in a trend analysis.

All analyses were performed with the SPSS computer program (SPSS Inc, Chicago, IL).
Fig 1. Analysis of outcome in 1,294 patients transplanted for CML in first chronic phase. Percentage of patients dying within 100 days (D100M) and 5 years' probability of patients dying of any transplant related mortality (TRM), dying of relapse (relapse), alive (SURV), and being well without leukemia (LFS) depending on grade of aGVHD (grade 0-IV).

and a decrease in RI, SURV, and LFS are better for patients with grade I aGVHD than for those with grade 0. From grade I onwards up to grade IV, they are continuously decreasing. This observation is true for patients below or above 20 years of age, independent of T-cell depletion and transplant source, ie, HLA-identical sibling, nonidentical family member or unrelated donor. The same pattern is observed in transplants before or after 1988 and independent of the time interval from diagnosis to transplant.

However, there is a different pattern for each endpoint investigated in the present analysis (Fig 1). D100M increases significantly from grade III onwards; TRM increases already from grade II GVHD. In contrast, RI decreases gradually with each grade. Because of this discordant effect of TRM and RI, LFS and SURV are best for patients with grade I aGVHD. These findings were consistent for all patients or when patients were analyzed separately in subgroups for age, sex, or donor type. Therefore, data for all patients were analyzed together. Table 3 gives the quantitative analysis of the influence of aGVHD grade by logistic regression with adjustment for the covariables age, sex, GVHD prevention, donor type, year of BMT, and interval from diagnosis to transplant on D100M, TRM, RI, LFS, and SURV. An additional trend analysis for relapse showed a significant linear decrease of relapse with grade of aGVHD ($P < .05$). So each grade higher for aGVHD is associated with a further reduction in risk of relapse.

In addition to the detailed 5-grade analysis, a series of two group settings for aGVHD absent or present were compared in Table 4. In both group settings the low grades were significantly different from the high grades; the only exception being one analysis of the relapse incidence (grade

<table>
<thead>
<tr>
<th>Grade aGVHD</th>
<th>N</th>
<th>D100M*</th>
<th>SURV†</th>
<th>TRM†</th>
<th>RI†</th>
<th>LFS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>462</td>
<td>17%</td>
<td>60%</td>
<td>28%</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>(429)</td>
<td>(15%)</td>
<td>(82%)</td>
<td>(27%)</td>
<td>(37%)</td>
<td>(46%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>335</td>
<td>13%</td>
<td>64%</td>
<td>27%</td>
<td>30%</td>
<td>51%</td>
</tr>
<tr>
<td>(288)</td>
<td>(11%)</td>
<td>(65%)</td>
<td>(25%)</td>
<td>(31%)</td>
<td>(52%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>264</td>
<td>19%</td>
<td>53%</td>
<td>43%</td>
<td>23%</td>
<td>44%</td>
</tr>
<tr>
<td>(236)</td>
<td>(17%)</td>
<td>(56%)</td>
<td>(40%)</td>
<td>(24%)</td>
<td>(46%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>110</td>
<td>38%</td>
<td>30%</td>
<td>68%</td>
<td>18%</td>
<td>26%</td>
</tr>
<tr>
<td>(98)</td>
<td>(35%)</td>
<td>(31%)</td>
<td>(67%)</td>
<td>(14%)</td>
<td>(28%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>123</td>
<td>70%</td>
<td>8%</td>
<td>92%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>(101)</td>
<td>(71%)</td>
<td>(9%)</td>
<td>(81%)</td>
<td>(9%)</td>
<td>(8%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,294</td>
<td>23%</td>
<td>52%</td>
<td>41%</td>
<td>31%</td>
<td>41%</td>
</tr>
</tbody>
</table>

* Incidence.
† Probability at 5 years.

Table 3. Relative Risk of aGVHD Score on Outcome for Patients With CML (n=1,294) After Allogeneic BMT in First Chronic Phase

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Grade aGVHD</th>
<th>Relative Risk (RR)</th>
<th>95% Confidence Interval for RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D100M</td>
<td>I</td>
<td>0.71</td>
<td>0.47-1.08</td>
<td>.11</td>
</tr>
<tr>
<td>II</td>
<td>1.07</td>
<td>0.71-1.64</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2.90</td>
<td>1.75-4.7</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11.2</td>
<td>6.89-18.21</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>TRM</td>
<td>I</td>
<td>1.17</td>
<td>0.86-1.61</td>
<td>.31</td>
</tr>
<tr>
<td>II</td>
<td>2.05</td>
<td>1.52-2.76</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3.95</td>
<td>2.84-5.50</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8.47</td>
<td>6.23-11.5</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>I</td>
<td>0.96</td>
<td>0.70-1.30</td>
<td>.77</td>
</tr>
<tr>
<td>II</td>
<td>0.83</td>
<td>0.57-1.23</td>
<td>.36</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0.74</td>
<td>0.35-1.35</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.31</td>
<td>0.67-1.31</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>LFS</td>
<td>I</td>
<td>0.99</td>
<td>0.64-1.23</td>
<td>.91</td>
</tr>
<tr>
<td>II</td>
<td>0.72</td>
<td>0.58-0.91</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0.42</td>
<td>0.32-0.56</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.19</td>
<td>0.15-0.25</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>SURV</td>
<td>I</td>
<td>1.01</td>
<td>0.78-1.32</td>
<td>.91</td>
</tr>
<tr>
<td>II</td>
<td>0.65</td>
<td>0.50-0.83</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0.35</td>
<td>0.26-0.47</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.16</td>
<td>0.12-0.21</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Relative risks are with respect to grade 0 of aGVHD and with adjustments for age, sex match, T-cell depletion, donor source, year of BMT, and interval from diagnosis to transplant.
Table 4. Relative Risk on Outcome in Several Two-Group Settings With Adjustments for Age, Sex Match, T-Cell Depletion, and Donor Source

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Two-Group Settings of aGVHD Grades</th>
<th>Relative Risk (RR)</th>
<th>95% Confidence Interval for RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D100M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs I</td>
<td>v I-IV</td>
<td>1.64</td>
<td>1.21-2.24</td>
<td>.001</td>
</tr>
<tr>
<td>0 vs II</td>
<td>v II-IV</td>
<td>2.97</td>
<td>2.24-3.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs III+IV</td>
<td>v III+IV</td>
<td>6.22</td>
<td>4.50-8.60</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I vs 0+II-IV</td>
<td>v 0+II-IV</td>
<td>2.45</td>
<td>1.70-3.35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TRM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs I</td>
<td>v I-IV</td>
<td>2.18</td>
<td>1.67-2.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs II</td>
<td>v II-IV</td>
<td>4.08</td>
<td>3.16-5.27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs III+IV</td>
<td>v III+IV</td>
<td>9.30</td>
<td>6.48-13.35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I vs 0+II-IV</td>
<td>v 0+II-IV</td>
<td>2.32</td>
<td>1.74-3.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs I</td>
<td>v I-IV</td>
<td>0.67</td>
<td>0.49-0.92</td>
<td>.01</td>
</tr>
<tr>
<td>0 vs II</td>
<td>v II-IV</td>
<td>0.48</td>
<td>0.33-0.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs III+IV</td>
<td>v III+IV</td>
<td>0.22</td>
<td>0.11-0.43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I vs 0+II-IV</td>
<td>v 0+II-IV</td>
<td>0.77</td>
<td>0.55-1.08</td>
<td>.12</td>
</tr>
<tr>
<td>LFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs I</td>
<td>v I-IV</td>
<td>0.61</td>
<td>0.48-0.79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs II</td>
<td>v II-IV</td>
<td>0.35</td>
<td>0.27-0.46</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs III+IV</td>
<td>v III+IV</td>
<td>0.16</td>
<td>0.11-0.23</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I vs 0+II-IV</td>
<td>v 0+II-IV</td>
<td>0.53</td>
<td>0.41-0.70</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

DISCUSSION

Twenty years ago, Glucksberg et al described the clinical manifestations of GVHD in human recipients of HLA-identical sibling donor marrow. With this analysis of 61 patients the classification of aGVHD was based on clinical manifestations of the main organs involved, skin, gastrointestinal tract, and liver into a scoring system (+ to ++++) for each organ and an overall grade from I to IV. It is interesting to observe that the GVHD incidence reported in his analysis (grade 0, 30%; I, 11%; II, 25%; III, 18%; IV, 16%), although showing a similar trend as our evaluation has shifted to less severe GVHD (grade 0, 36%; II, 20%; III, 9%; IV, 10%; P = .005) compared with Glucksberg et al’s results, probably because of improved GVHD prophylaxis and despite a proportion of BMT (10%) performed with nonidentical related and unrelated donors. The predictive value of the aGVHD grading for mortality rate already described by Glucksberg et al\(^6\) (grade 0 GVHD, 44%; I, 43%; II, 80%; III, 91%; IV, 90%) with best survival for patients with grade I has remained, but the outcome has improved since except for grade IV. This finding can be explained by the fact that grade IV is mainly assigned retrospectively to patients who die with aGVHD within 100 days (grade 0 GVHD, 39%; I, 32%; II, 45%; III, 64%; IV, 93%).

The findings on incidence and severity in this study confirmed earlier reports, but also showed unexpected findings. aGVHD is clearly more frequent and more severe in patients receiving nonidentical family or unrelated transplants. As expected, the same holds true for patients given non—T-cell—depleted transplants. In contrast, we observed the same incidence and severity of aGVHD in patients younger than 20 years compared with older than 20 years. The effect of age on GVHD described previously\(^6,10\) might be lost in the present patient population because only a few younger patients (12% <20 years) are reported. Interestingly, despite similar incidence and severity of GVHD in younger patients, TRM was lower than in older patients. This means that younger patients tolerate aGVHD and its treatment better. A similar observation concerns male patients receiving female donor marrow. They have the same incidence and severity of aGVHD as other patients, but, as previously reported, a higher TRM.\(^11\) Factors other than aGVHD must account for the higher TRM.

With the introduction of new GVHD prevention methods, such as cyclosporin and T-cell depletion and the recognition by the statistical analysis when grade I is compared in a Cox regression analysis with grades 0 and II (Table 5).

Table 5. Relative Risk of aGVHD Grade I vs Grade 0 + II

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative Risk (RR)</th>
<th>95% Confidence Interval for RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D100M</td>
<td>0.69</td>
<td>0.47-1.00</td>
<td>.05</td>
</tr>
<tr>
<td>TRM</td>
<td>0.71</td>
<td>0.52-0.96</td>
<td>.02</td>
</tr>
<tr>
<td>RI</td>
<td>1.03</td>
<td>0.72-1.49</td>
<td>.86</td>
</tr>
<tr>
<td>LFS</td>
<td>1.33</td>
<td>1.00-1.73</td>
<td>.05</td>
</tr>
</tbody>
</table>

Analysis restricted to 1,061 patients with grade 0, I, or II.
of additional clinical signs of aGVHD, such as nausea, vomiting, and upper gastrointestinal tract symptoms, the value of the Seattle criteria has been debated. This uneasiness has been further supported by a study conducted by the IBMTR in which BMT teams were asked to grade a simulated patient according to their criteria.\textsuperscript{12} There was significant discordance for individual patients, but overall good agreement for the categories absent, moderate, or severe aGVHD. In many reports aGVHD is therefore only presented as absent, moderate, or severe or as grade less than II versus \( \geq II \). No studies have assessed the predictive value of the detailed grading system.

We have profited from the fact that a large cohort of patients transplanted for CML and reported to the EBMT was analyzed, updated, and verified by participating teams. We examined whether in this cohort the grade of aGVHD had any impact on outcome. If so, we wanted to know whether an identical or different impact on the five endpoints measured was observed.

In the late 1970s, GVHD was reported to contribute to improved survival after allogeneic BMT.\textsuperscript{1,3} Survival among 163 patients alive without disease 150 days after BMT for acute leukemia in remission or in relapse was best in patients with GVHD (acute and chronic) in comparison to patients without GVHD. More recently, the influence of acute and chronic GVHD on relapse and survival was examined in a larger group of patients (\( n = 1,202 \)).\textsuperscript{2} Sullivan et al.\textsuperscript{2} were able to show that acute and chronic GVHD were associated with a durable antileukemic effect and improved survival in patients transplanted in advanced stage of ALL and CML.

However, among patients with ALL in first remission or CML in chronic phase, mild to severe GVHD (grades II-IV) had an adverse effect on survival and they failed to observe a positive influence on relapse. A few years later, this finding was supported in more detail by Nash et al.,\textsuperscript{9} showing a negative effect of the different aGVHD grading (O-I, II, and III-IV) on survival.\textsuperscript{9} In our analysis, in which each GVHD grade has been analyzed separately in a large population of patients with a single disease transplanted at the same stage of the disease, we have confirmed the negative influence of GVHD grades II, III, and IV on survival. For the first time in patients with CML in chronic phase we can now also document a positive effect of grade I GVHD. This finding might be explained by the decreased RI and unchanged TRM in comparison to patients without GVHD. Decreased RI might be caused by the graft-versus-leukemia (GVL) effect of GVHD.\textsuperscript{14-17} The findings of minor histocompatibility antigen-specific cytotoxic T cells in vitro that can recognize leukemic cells lend support to our clinical findings. For aGVHD grades higher than I, the decreased RI is offset by the increased TRM resulting in overall lower LFS. Vice versa, the lower incidence and severity of aGVHD in patients with T-cell depletion is offset by the loss of GVL and increased relapse rate.

Results of the present analysis therefore validate the initial Seattle classification and their predictive value. It is comforting to see that incidence and severity of GVHD have declined since the initial report of Glucksberg et al.\textsuperscript{10} and that survival for any grade has substantially improved. The data confirm the relevance of aGVHD grading not only for SURV and LFS, but also for D100M, TRM, and RI. GVHD has a different impact on D100M than on TRM. Grade II GVHD does not influence D100M, although it clearly does influence TRM. This difference might be explained by the possible complications associated with aGVHD, such as chronic GVHD, infections, and interstitial pneumonia resulting in the death of the patients after day 100.\textsuperscript{18} For RI there is no cut-off point. There is a continuous decrease of RI with increasing GVHD, suggesting that GVL parallels GVHD in its intensity. As a consequence of the divergent effect of TRM and RI, LFS and SURV appear superior for patients with grade I aGVHD. This potential beneficial effect of grade I aGVHD on LFS justifies attempts to induce limited aGVHD in autologous BMT. Overall, our findings show that the Seattle GVHD grading remains valid after more than 20 years after its first description and that the simplification to less than II and \( \geq II \) is not justified, because patients with different GVHD grades have different outcomes. Depending on the endpoint analyzed, grading should be reported in detail for data comparison.

**APPENDIX**

**List of participating teams (no. of patients reported):**

- RPMS Hammersmith Hospital, London, J.M. Goldman (158)
- Ospedale San Martino, Genova, A. Bacigalupo (109)
- Huddinge Hospital, Huddinge, G. Gahrton (64)
- Hospital Clinic, Barcelona, E. Carreras (62)
- Hospital San Orsola, Bologna, G. Bandini (59)
- Kantonsklinik, Basel, A. Gratwohl (50)
- University Hospital, Niort, T. de Witte (47)
- Universit"{a}t degli Studi Sapienza, Rome, W. Arceci (41)
- H"{o}pital Henri Mondor, Cr"{e}teil, J. Vernet (38)
- Royal Free Hospital, Hampstead, London, H.G. Prentice (34)
- Ospedale di Careggi, Firenze, P. Rossi-Ferini (29)
- University Hospital, Leiden, R. Willemze (28)
- University Hospital, Leuven, M. Boogaerts (26)
- Ospedale Civile, Pescara, G. Torlontano (26)
- Medical School of Hannover, Hannover, H. Link (24)
- Med Klinik III, Klinikum Grosshadern, M"{u}nchen, H. Kolb (24)
- Cliniques Universitaires St Luc, Brussels, A. Ferrant (23)
- Hospital “Marques de Valdecilla,” Santander, A. Iriondo (22)
- H"{o}pital A. Michallon, Grenoble, D. Hollard (22)
- University of Helsinki, Helsinki, T. Ruutu (22)
- H"{o}pital Saint Louis, Paris, E. Gluckman (21)
- Universit"{a}t Ulm, Ulm, R. Arnold (19)
- Royal Marsden Hospital, Sutton, Surrey, R. Powles (16)
- Inst Paoli Calmettes, Marseille, D. Maraninchi (16)
- Daniel Den Hoed Cancer Center, Rotterdam, J. Cornelissen (16)
- Rikshospitalet, Oslo, S. Evensen (15)
- Heinrich-Heine-Universit"{a}t, D"{u}sseldorf, V. Runde (14)
- Inst. SciencMediche, Milano, G. Lambertenghi-Deliuers (12)
- King Faisal Specialist Hospital, Riyadh, P. Ernst (12)
- University College Hospital, London, A.H. Goldstone (11)
- Klinikum Rudolf Virchow, Berlin, W. Siegert (11)
- H"{o}pital Jean Minjoz, Besancon, J. Cahn (10)
- University Hospital, Utrecht, L. Verdonck (10)
- Royal Infirmary, Edinburgh, A. Parker (9)
- Hospital Reina Sofia, Cordoba, A. Torres Gomez (9)
- H"{o}pital du Haut Levêque, Pessac, J. Rebffers (9)
- Rigshospitalet, Copenhagen, N. Jacobsen (8)
- Christian-Albrechts-Universit"{a}t, Kiel, N. Schmitz (8)
- Ibn-i-sina Hospital
REFERENCES


