Marrow Transplantation From Unrelated Donors for Treatment of Hematologic Malignancies: Effect of Mismatching for One HLA Locus


One hundred twelve patients less than 36 years old received marrow grafts from unrelated donors as treatment for hematologic malignancy. Seventy donor/recipient pairs were phenotypically identical for HLA-A, -B, and -D, while 42 had a "minor" disparity at one HLA locus. There was an increase in the risk of acute graft-versus-host disease (GVHD) in patients receiving HLA-partially matched grafts compared with those receiving HLA-matched grafts (51% ± 36% probability of grades III-IV acute GVHD). However, in this cohort of patients, there was no significant difference in survival (at 1.5 years, 46% ± 51% for good-risk patients, 44% ± 30% for poor-risk patients). This finding suggests that some degree of HLA disparity can be tolerated in young patients transplanted from unrelated donors for malignant disease, thus making transplantation an option available to larger numbers of patients.

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During the past 2 decades marrow transplantation has become accepted as the most effective treatment for many hematologic malignancies. However, most patients do not have a suitable marrow donor within the family because fewer than 35% of patients have an HLA-identical sibling. Although it is possible to perform successful transplants across HLA differences within families, the risk of complications rises rapidly with increasing disparity, limiting this option to no more than 5% of patients. Therefore, several transplant centers have tested the feasibility of unrelated marrow transplantation, an endeavor made possible by the availability of large registries of HLA-typed individuals willing to serve as donors.

With the development of a national registry for facilitating unrelated donor searches, The National Marrow Donor Program (NMDP), it is possible to find an HLA-A, -B, -DR, -D phenotypically identical donor for approximately 25% of patients (NMDP, unpublished data, April 1992). Although the NMDP now contains HLA typing data for more than 500,000 volunteers, it may never be possible to find an HLA-identical donor for all patients even if the registry is enlarged to include more than a million donors. We show here that the potential number of unrelated donor transplants can be expanded by relaxing the stringency of HLA matching criteria. We performed transplants for 42 patients using HLA-partially compatible unrelated donors; similar survival was demonstrated when results in these patients were compared with results of 70 transplants from HLA-matched unrelated donors.

MATERIALS AND METHODS

Donor and patient selection. All study patients were referred to the Fred Hutchinson Cancer Research Center for treatment of a hematologic malignancy and were eligible for a marrow transplant protocol, but lacked an appropriate family member donor. Each patient was offered an unrelated donor search. HLA-A, -B, -DR, -D phenotypically identical donors were found for 70 patients. Phenotypic identity for HLA-D (Dr-Dw23) was determined primarily by typing with HLA homozygous cells as previously described. In cases where a clear assignment of an HLA-D specificity could not be made, additional analyses were undertaken with selected T-cell clones, with restriction fragment length polymorphism DNA studies, and/or with HLA-DR-specific oligonucleotide probes.

If an HLA-A, -B, -DR, -D phenotypically identical donor was not identified, and if the patient was less than 36 years old, the search was extended to include potential donors incompatible for no more than one minor mismatch at the HLA-A, -B, or -D locus. An HLA class I minor mismatch was defined as disparity between two distinct but cross-reactive HLA-A or -B locus antigens as defined by the NMDP. An HLA-DR minor mismatch was defined as a match for HLA-DR by conventional serologic methodology but disparity between two distinct HLA-D specificities. For example, a minor mismatch could exist when both patient and donor were DR4, but were further typed as Dw4 and Dw10. In cases of homozygosity of patient and/or donor, homozygosity was confirmed by patient family study and/or DNA studies for Class II, and/or isoelectric focusing for Class I.

Patients. Between May 8, 1985 and July 27, 1990, 112 patients less than 36 years old with hematologic malignancies received marrow grafts from unrelated donors (Table 1). Seventy of these unrelated donor/recipient pairs were phenotypically identical for HLA-A, -B, -D, and 42 had a minor mismatch for a pair of antigens encoded by a single locus. At the time of the initial study, 42 of the 112 donor/recipient pairs were thought to differ for only one locus: 14 differed at the A locus, 7 at the B locus, and 21 for the D region. After more detailed studies were completed, one pair was found to be different at both D loci, and another was found to differ for both the B and D loci. Both patients remained in the analysis. In six cases, either donor or patient was homozygous at the mismatched locus, one of each case at each of the three loci. For purposes of this analysis, the patient and donor were considered to be mismatched if only the donor was homozygous at the mismatched locus. The patient and donor were considered matched if the patient was homozygous because recipient incompatibility but not donor incompatibility increases the risk of graft-versus-host disease (GVHD).
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Phenotypic Matching for HLA-A, -B, and -D</th>
<th>Identical</th>
<th>Partial Match</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis [no. of patients, (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor risk</td>
<td>25 (17)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>CML-AP, -BC</td>
<td>18 (28)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Good risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CML-OP, BC/Rem</td>
<td>27 (39)</td>
<td>16 (38)</td>
</tr>
<tr>
<td>AL-Rem</td>
<td>9 (13)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>42</td>
</tr>
<tr>
<td>Search interval (d)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Patient age (yrs)</td>
<td>183</td>
<td>224</td>
</tr>
<tr>
<td>25th, 50th, 75th percentiles</td>
<td>28-1,411</td>
<td>34-1,715</td>
</tr>
<tr>
<td>Donor age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25th, 50th, 75th percentiles</td>
<td>32, 38, 44</td>
<td>30, 39, 43</td>
</tr>
<tr>
<td>CMV serology [no. of patients, (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient+/donor+</td>
<td>11 (15)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Patient+/donor-</td>
<td>20 (29)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Patient-/donor+</td>
<td>7 (10)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Patient-/donor-</td>
<td>32 (46)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Marrow cells infused, mean x 10^6/ kg</td>
<td>3.8 (0.4-46.2)</td>
<td>3.6 (1.5-10.0)</td>
</tr>
</tbody>
</table>

Transplant procedure. All patients were prepared for transplantation according to protocols appropriate for the underlying disease and disease stage, irrespective of donor match or mismatch. In general, patients received two doses of intrathecal methotrexate, cyclophosphamide 60 mg/kg/d for 2 days, then fractionated or unfractiated total body irradiation (TBI) 10 to 15.75 Gy total dose. The TBI regimen varied according to the primary disease and disease stage. After the completion of chemotherapy and TBI, unmodified (ie, non-T-cell depleted) donor marrow cells were infused on day 0. All patients received a combination of methotrexate and cyclosporine for acute GVHD prophylaxis. The data were analyzed as of March 1992. With a medium follow-up of 2.4 years for surviving patients. All patients gave written consent and were treated under protocols approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Statistical considerations. Although assignment of patients was solely dependent on whether a matched or partially matched donor was found, it is possible that there were biases not apparent or accounted for. Myeloid engraftment was considered to have occurred on the first of 3 consecutive days that the absolute neutrophil count was greater than 10^9/L. Failure of donor myeloid engraftment was evaluated in patients who survived a minimum of 21 days and had no evidence of clinical leukemic relapse. Kaplan-Meier estimates were used to display survival and acute GVHD incidence. The severity of acute and chronic GVHD was staged and graded according to previously published criteria. Cumulative incidence curves were used to represent occurrence of chronic GVHD and relapse. Cox proportional hazards regression models were used to examine the effects of minor mismatch on acute GVHD incidence, chronic GVHD incidence, and survival. We attempted to adjust for potential confounding factors by including them as covariates if they appeared to make a contribution to the model. Factors considered for these models included diagnosis and stage of disease, donor search interval, disease duration, patient and donor age, patient and donor cytomegalovirus (CMV) serology status before transplant, patient sex, donor sex, donor parity, TBI dose, placement in a laminar air flow room, and marrow cell dose.

**Fig 1.** Probability of attaining a sustained granulocyte count of 1,000/mm^3 as a function of time after transplantation. Tick marks represent patients who died before attaining 1,000/mm^3 granulocytes.

**Fig 2.** Probability of developing acute GVHD grades II-IV as a function of time after transplantation. Tick marks represent patients who died before developing acute GVHD ≥ II.

**Fig 3.** Probability of developing acute GVHD grades III-IV as a function of time after transplantation. Tick marks represent patients who died before developing acute GVHD ≥ III.
RESULTS

Engraftment. One hundred six of the 112 patients receiving transplants were informative for engraftment. The overall probability of failure to engraft was 3.1% (2 of 65) in the matched group, and 4.9% (2 of 41) in the partially matched group. There was no difference in the two groups in the median time to reach a granulocyte count of 1,000/mm\(^3\) (Fig 1). Of the four patients who did not achieve donor myeloid engraftment, three died without recovery of myeloid function, and one had autologous reconstitution followed by leukemia relapse and subsequent second unrelated transplant. An additional six patients died before achieving a count of 1,000 granulocytes/mm\(^3\), but before death had evidence of engraftment by marker analysis and/or granulocytes increasing above 100/mm\(^3\).

Acute GVHD. The incidence of grades II-IV acute GVHD was 78% (95% confidence interval [CI] 67% to 88%) for HLA-A, -B, -DR, -D phenotypically identical transplants, and 94% (95% CI 85% to 99%) for partially matched transplants (P < .001) (Fig 2). The risk of grades III-IV acute GVHD was 36% (95% CI 26% to 48%) for phenotypically identical transplants, and 51% (95% CI 37% to 66%) for the partially matched group (P = not significant) (Fig 3). In a multivariate analysis (not shown), the presence or absence of potential confounding factors did not influence the relative risk estimate for mismatch effect on acute GVHD (RR = 2.2, P < .001). When analyzed separately, HLA Class I and Class II mismatches were associated with similar acute GVHD rates (data not shown). The higher risk of acute GVHD in the mismatches did not adversely impact day 150 survival, which was 23 of 42 (55%) versus 41 of 70 (59%) for the matches.

Chronic GVHD. At day 100 posttransplant, 46 of 70 (66%) matched recipients and 27 of 42 (64%) partially matched recipients were alive with sustained engraftment and were relapse-free, and hence were evaluable for development of chronic GVHD. The cumulative incidence of clinical extensive chronic GVHD was 61% (95% CI 45% to 76%) for phenotypically identical recipients, and 74% (95% CI 59% to 89%) for partially matched recipients (Fig 4). A multivariate analysis (not shown) with pre-existing acute GVHD either
included or excluded from the model could not detect a significant effect of HLA mismatch on the risk of chronic GVHD. There was a trend for a greater probability of death subsequent to developing chronic GVHD in the partially matched group (11 of 20, 55%) compared with the matched group (9 of 28, 32%), but this apparent difference was not statistically significant (P = .12). At the time of analysis, 22 of 27 matches (81%) and 13 of 16 mismatches (81%) had Karnofsky scores of 90 or 100. A more thorough analysis of this complication is underway.

Relapse. There was a trend for the probability of relapse to be greater in the matched group (23%, 95% CI 11% to 30%) as compared with the partially matched group (12%, 95% CI 2.4% to 19%) but this difference was not significant (P = .19) (Fig 5).

Survival. Kaplan-Meier projected survival at 1.5 years was 51% (95% CI 34% to 64%) and 46% (95% CI 27% to 64%) for matched and partially matched “good-risk” patients (acute leukemia in remission, chronic myelogenous leukemia-chronic phase [CML-CP], myelodysplastic syndrome, lymphoma), respectively (Fig 6). Survival at 1.5 years for “poor-risk” patients (acute leukemia in relapse, CML-accelerated phase [AP]/blast crisis [BC]) was 30% (95% CI 15% to 47%) and 44% (95% CI 20% to 66%) for matched and partially matched patients, respectively (Fig 7). A multivariate analysis (Table 2) showed no association between HLA disparity and survival (RR = 1.1, P = .61).

DISCUSSION

Marrow transplantation from unrelated donors has become accepted therapy for patients lacking an appropriate family member donor. Despite efforts to increase the size of current registries, to broaden their racial and ethnic diversity, and to establish collaborations between registries in other countries, it is likely that some patients will never be able to find a fully HLA-matched donor. Therefore, it is important to determine whether transplantation from a less than fully HLA-matched unrelated donor might be feasible. If so, this strategy would increase the fraction of patients for whom a suitable donor can be found. The rationale for this approach stems from studies which involve related donors and which demonstrate that disease-free survival after haploidentical one HLA-A,-B, or -D locus incompatible transplants is indistinguishable from that observed after HLA-genotypically identical transplantation.6,7 Furthermore, an analysis of these related one-locus partially matched transplants has indicated that the risk of acute GVHD may be less when the disparate antigens fall within a cross-reactive group (CREG) than when the disparate antigens are not serologically cross-reactive.28 Other groups have also shown a high risk of acute GVHD in patients receiving grafts from HLA mismatched unrelated donors.12,13

In the current study there is no difference in survival between matched and partially matched groups, although there was a clear increase in risk for acute GVHD in the partial matches. This seeming paradox is explained by a similar day 150 survival in the two groups, with perhaps some contribution of a graft-versus-leukemia effect.29,30 It is possible that in other groups of patients such an equivalency in survival would not be seen. For instance, in patients transplanted for nonmalignant diseases, the graft-versus-host reaction would likely have only a negative impact on survival. Furthermore, in patients older than 35 years of age, acute GVHD may have a greater impact on morbidity; thus, the increased incidence of acute GVHD seen in partial matches might adversely affect survival.

The data presented here suggest that the criteria for choosing unrelated donors can include minor mismatches, at least in younger patients. This should make it possible not only to identify donors for more patients, but also to expand the number of potential donors for each patient. Furthermore, for particular patients at high risk of disease progression, an immediate transplant from a partially matched donor might be preferable to a prolonged search for a full match.

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