T-Cell-Depleted Allogeneic Bone Marrow Transplantation in Adults With Acute Nonlymphocytic Leukemia in First Remission


We prospectively evaluated the efficacy of T-cell-depleted bone marrow transplantation (BMT) in adults with de novo acute nonlymphocytic leukemia (ANLL) in first complete remission (CR), with regard to relapse-free survival and incidence of graft-versus-host disease (GvHD). Thirty-one patients older than 16 years (range, 16.5 to 43.2) received T-cell-depleted grafts for this purpose from related HLA/MLC-compatible donors. Twelve of the patients were older than 30 years at the time of transplantation. Patients were prepared with hyperfractionated total body irradiation (HFTBI; 1,375 to 1,500 cGy) and high-dose cyclophosphamide (120 mg/kg). T cells were removed from the marrow grafts by a two-step soybean lectin agglutination and sheep red blood cell (sRBC)-rosette procedure, achieving a 2.5- to 3-log depletion of clonable T lymphocytes. No additional prophylaxis against GvHD was administered. The median age at transplantation was 28.8 years; the median interval from diagnosis to transplantation was 3.8 months, and from CR was 2.7 months. Seventy-four percent received consolidation after remission induction therapy. The product-limit estimate of disease-free survival (DFS) at 3 years is 45% (95% confidence interval [CI], 24% to 66%), and the cause-specific probability of relapse is 13%. The median follow-up of the survivors is 72 months (range, 34.5 to 95.6). Median time to achieve a sustained absolute neutrophil count of 500 or greater was 16 days, and to maintain an untransfused platelet count of 20,000 or greater was 20 days. Five patients suffered immune-mediated graft rejection. Three patients developed grade I to II acuté GvHD limited to the skin, which resolved promptly with brief courses of systemic steroids. None of the patients has developed clinically apparent chronic GvHD or a secondary lymphoproliferative disorder, and no patient is receiving immunosuppressive therapy. T-cell-depleted BMT by the method reported here is a favorable option as postremission therapy for adults with de novo ANLL in first remission who have an HLA/MLC-compatible related donor, and it is not associated with an increased risk of relapse posttransplant.

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Approximately 60% to 85% of adult patients with acute nonlymphocytic leukemia (ANLL) achieve a first complete remission (CR) following treatment with current chemotherapeutic regimens that typically include an anthracycline and cytosine arabinoside.1,2 Most clinical investigators also agree that additional chemotherapy in the form of either consolidation or intensification is necessary to prevent relapse once remission has been achieved.1,3 The nemesis of this initial success is that most of these patients eventually relapse, yielding a durable disease-free survival (DFS) in most series of approximately 10% to 25%,1,2 although rates as high as 45% have been reported.4 Bone marrow transplantation (BMT), initially used as salvage therapy for patients with advanced hematologic malignancies, is becoming increasingly accepted as postremission therapy for patients achieving a first CR.5-13 The application of allogeneic grafts is still largely limited to those patients for whom an HLA/MLC-compatible related donor is available. Their use is also limited by patient age, as older patients are at higher risk for the development of graft-versus-host disease (GvHD), a principal cause of both primary and secondary morbidity and mortality.14,15 Pharmacologic prophylaxis has significantly reduced the incidence of severe grade II to IV acute GvHD, but this has not affected the incidence of chronic GvHD and its long-term secondary immunosuppressive and functional sequelae.14 Based largely on the initial success of T-cell-depleted marrow grafts from haploidentical parental donors transplanted to children with severe combined immune deficiency,16 we undertook T-cell-depleted BMT in adult patients with de novo ANLL in first CR who had HLA/MLC-compatible related donors. The goal was to reduce the incidence of GvHD and its complications in order to improve the results of transplants in older or partially mismatched patients. Here we report the results of this transplant approach in a group of 31 patients above the age of 16 years. Our results demonstrate a marked reduction in the incidence of both acute and chronic GvHD. As in other series,17-20 this advantage has been offset by an increased incidence of graft failure. However, bone marrow grafts used in the treatment of de novo ANLL in first CR, but depleted of T cells by the method reported here, are not
associated with an increased incidence of posttransplant relapse.

MATERIALS AND METHODS

Patient characteristics. Patients with de novo ANLL were eligible for entry into this study after achieving first CR if they had related HLA/MLC-compatible donors (serologic identity for HLA-A,B,C,DR and mutual nonreactivity in mixed leukocyte culture) and no severe cardiac, hepatic, or renal dysfunction that would have precluded their proceeding with BMT. Thirty-one consecutive patients above the age of 16 years fulfilled these criteria. Patients were referred from Memorial Sloan-Kettering Cancer Center, as well as from outside physicians, although all patients received standard induction therapy consisting of an anthracycline and cytosine arabinoside. Seventy-four percent of the patients received consolidation following remission induction chemotherapy before proceeding with transplantation. The 31 patients under study received T-cell-depleted allogeneic bone marrow grafts from HLA/MLC-compatible related donors during the period January 12, 1984 to March 1, 1989. The median age of the patients was 28.8 years, and 12 of these patients were older than 30 years at the time of transplantation. Pretransplant patient characteristics are detailed in Table 1.

Preparative regimen. Patients received myeloablative cytoreduction consisting of hyperfractionated total body irradiation (HFTBI) followed by high-dose cyclophosphamide. HFTBI was administered in fractions of 125 cGy at a dose rate of 8 to 20 cGy/min, three fractions per day, at 5- to 7-hour intervals for 4 days. Ten patients transplanted through early 1985 received 11 fractions (1,375 cGy total), and 21 patients transplanted since May 1, 1985 received 12 fractions (1,500 cGy total). All patients had protective lung shielding to reduce the effective dose to the lung parenchyma to approximately 900 cGy; overlying ribs received an additional 600-cGy boost using high-energy electrons to increase the total dose to the chest wall to approximately 1,500 cGy. Male patients also received an additional 400 cGy testicular boost with electrons in a single fraction on the first day of HFTBI.

Following completion of HFTBI, patients received high-dose cyclophosphamide in two equal doses of 60 mg/kg/d. Electrocardiographic monitoring, as well as aggressive hydration and electrolyte replacement, was used according to standard practice.

Bone marrow collection, T-cell depletion, and transplantation. Normal bone marrow was obtained from the designated donor under general anesthesia by multiple aspirations from the anterior and posterior iliac crests bilaterally. Freshly obtained donor marrow was depleted of T cells by a two-step soybean lectin separation step that achieves a 2.5- to 3-log depletion of clonable T lymphocyte. The positively selected by-product of the first separation step was designated the SBA+ fraction; it was γ-irradiated (4,000 cGy, 137 Cs) to inactivate alloreactive lymphocytes and was administered as a first fraction to the patient. This was done empirically to provide a source of radiosensitive accessory cells and to bind any persistent circulating antileukocyte antibodies. The negatively selected final fraction was designated SBA-E-, and was administered to the patient as the T-cell–depleted bone marrow stem cell fraction. Marrow was infused via central venous access.

The day of the marrow collection was designated day 0. Patients received the freshly T-cell–depleted grafts within 12 hours of collection. Twenty-nine of the 31 patients received no additional prophylaxis against GvHD; two patients received antithymocyte globulin (ATG) and steroids, nominally administered for rejection prophylaxis (see below). Rejection prophylaxis. During the period of this study, certain factors were identified as predictors of increased risk for rejection of T-cell–depleted BMT. However, only two of these 31 recipients of T-cell–depleted grafts were transplanted after completion of that analysis and thereby identified as being at risk. These two patients were treated under a concurrent rejection prophylaxis protocol using a combination of ATG (15 mg/kg every other day) and methylprednisolone (2 mg/kg/d) from day +5 through day +19 with a rapid steroid taper thereafter.

GvHD evaluation and management. GvHD was diagnosed clinically, confirmed pathologically by skin or mucosal biopsy, and classified according to standard criteria. Only patients surviving 30 days or longer could be evaluated for acute GvHD, unless it had already become clinically apparent by the time they died; thus, five patients could not be evaluated. Patients who developed acute GvHD were treated with methylprednisolone (2 mg/kg/d) and prophylaxis against pneumocystis carinii pneumonia before the transplant and again from the third through ninth months inclusive posttransplant, once stable engraftment was achieved (defined as an untransfused platelet count ≥ 100,000); (2) acyclovir prophylaxis

Table 1. Pretransplant Patient Characteristics

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Median 28.8</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean 29.1 ± 8.6</td>
</tr>
<tr>
<td>16-20</td>
<td>6</td>
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<tr>
<td>20-29</td>
<td>13</td>
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<td>30-39</td>
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<td>F → M</td>
<td>8</td>
</tr>
<tr>
<td>F → F</td>
<td>6</td>
</tr>
<tr>
<td>M → M</td>
<td>3</td>
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<tr>
<td>M → F</td>
<td>14</td>
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</tr>
<tr>
<td>M5</td>
<td>3</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>5</td>
</tr>
<tr>
<td>No. of induction courses to achieve CR</td>
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</tr>
<tr>
<td>1</td>
<td>21</td>
</tr>
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<td>1</td>
<td>16</td>
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<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Elapsed time to BMT (mo)</td>
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<tr>
<td>From Dx</td>
<td>3.8</td>
</tr>
<tr>
<td>(range)</td>
<td>(1.9-8.3)</td>
</tr>
<tr>
<td>From CR</td>
<td>2.7</td>
</tr>
<tr>
<td>(Range)</td>
<td>(0.9-7.2)</td>
</tr>
</tbody>
</table>

Abbreviations: FAB, French-American-British; Dx, diagnosis.
for prevention of DNA herpesvirus infections (eg, herpes simplex virus [HSV], cytomegalovirus [CMV]); and (3) CMV-seronegative
blood product transfusions to all CMV-seronegative patients regardless of marrow donor CMV serology.

Informed consent. All investigations were performed after proto-
col approval by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center, and in accord with an assurance
filed with and approved by the US Department of Health and Human Services. After the potential risks and benefits were
explained, all patients and donors, or the parents/guardians of
minors, signed informed consent.

Data collection and statistical methods. Engraftment was deter-
mimed directly by evaluation of cytogenetic markers (ie, sex
chromosome differences between donor-recipient pairs, Q-band-
ing to assess donor-recipient DNA polymorphisms, and/or pres-
ence or absence of leukemic karyotypes post-BMT). Engraftment
and disease status were also assessed in standard fashion by the
recovery of peripheral blood counts without transfusion support
and evaluation of bone marrow aspirates obtained at regular
intervals post-BMT. Thereafter, patients have received at least
annual follow-up evaluation.

Analyses were performed as of January 1, 1992. The probability
of disease-free survival (DFS) and time to relapse were estimated
using the methods of Kaplan-Meier and competing risks, respec-
tively. Intervals were calculated from the date of BMT.

RESULTS

Engraftment. Twenty-six of the 31 patients engrafted
following T-cell–depleted marrow transplants. These pa-
tients achieved an absolute neutrophil count ≥0.5 × 10^9/L
for 3 consecutive days at a median interval of 16 days
posttransplant (range, 13 to 27), and ≥1.0 × 10^9/L at a
median interval of 21 days (range, 13 to 43). Sustained
platelet counts of 20 × 10^9/L or greater for 3 consecutive
days without transfusion support were reached at a median
interval of 20 days (range, 10 to 51). These time points are
not significantly different from those observed in recipients of
unmodified grafts, consistent with published results from
our overall series of patients.

Five of the 31 recipients of T-cell–depleted transplants
suffered immune-mediated early graft failures posttrans-
plantation (one each by day +15, +25, +35, +38, and
+52). In previous reports, we have documented an in-
creased risk of rejection in adult recipients of male and
older female donor transplants, regardless of recipient sex.
In this series, four of 17 recipients of male donor
grafts (three M → F, one M → M) experienced immune-
mediated graft failure. The donor for the remaining patient
was a 50-year-old woman (F → M). These five patients
were transplanted before the identification of predictive
factors for rejection and therefore did not receive prophy-
laxis against this complication.

DFS and overall survival. The Kaplan-Meier product-
limit estimate of the probability of DFS at 3 years is 45%
(95% confidence interval [CI], 24% to 66%), as illustrated
in Fig 1. The median follow-up for the survivors is 72.1
months (range, 34.5 to 95.6). Calculated overall survival is
essentially identical to DFS and is not shown. Among the 12
patients transplanted between the ages of 30 and 43 years,
seven survive free of disease. There was no significant
difference in the probability of DFS for patients trans-
planted above and below the median age of 28.8 years.

Causes of treatment failures. A major cause of nonleuke-
mic deaths in this series was immune-mediated graft
failure, which occurred in five patients. Other causes of
death included interstitial pneumonitis (two due to P
carinii at 2.6 and 3.6 months post-BMT in the setting of
probable noncompliance with prophylaxis; one due to CMV
at 2.7 months post-BMT), as well as a single fatal case of
aspergillus pneumonia at 3.3 months post-BMT. Most of
these patients received transplants before the standard use
of combination 9-(1,3-dihydroxy-2-propoxy methyl)guanine
(DHPG) and intravenous y-globulin therapy for docu-
mented CMV disease, but none of the survivors developed
viral or idiopathic interstitial pneumonitis. There were
no deaths directly attributable to septicemia. The causes
of treatment failure are summarized in Table 2.

Table 2. Causes of Treatment Failure

<table>
<thead>
<tr>
<th>Cause</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Primary graft failure</td>
<td>5</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>3</td>
</tr>
<tr>
<td>Aspergillus pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>2</td>
</tr>
<tr>
<td>Other treatment-related toxicity</td>
<td>1</td>
</tr>
<tr>
<td>Relapse</td>
<td>4</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1</td>
</tr>
</tbody>
</table>

*Two cases due to P carinii at 2.6 and 3.8 months post-BMT in the setting of probable noncompliance with prophylaxis; one case due to CMV at 2.7 months post-BMT.
†Three of these four patients required two or more inductions to achieve first CR.
Four patients relapsed in this series (one each at 5.2 months and 7.4 months, and two at 6.1 months). Three of these patients had required two or more courses of induction to achieve first CRs, the durations of which were only 0.9 to 1.6 months before proceeding to transplantation.

There was a trend toward lower probability of DFS among all patients who required two or more courses of induction chemotherapy to achieve CR (1 course, 52% ± 24% DFS; ≥2 courses, 30% ± 30% DFS; P = .35), but the small samples prevent demonstration of statistical significance. We also estimated the probability of leukemic relapse in the presence of the competing risks of treatment failures due to nonleukemic causes. The estimated probability of relapse in this group of adults with de novo ANLL in first CR is only 13% (95% CI, 1% to 25%) at 3 years following related HLA/MLC-compatible T-cell-depleted marrow transplantation (Fig 2). To date, all relapses have occurred within the first year following transplantation.

Incidence of GvHD. Three of 26 recipients of T-cell-depleted BMT who could be evaluated developed acute grade I (1 patient) or grade II (two patients) GvHD. These cases were limited entirely to the skin and resolved with a brief course of systemic steroids. None of the patients have developed clinically apparent chronic GvHD, and none have received any further pharmacologic immunosuppression.

Performance status of disease-free survivors. All of the disease-free survivors have Karnofsky performance status scores of 100%.

DISCUSSION

Thirty-one adult patients over the age of 16 years with de novo ANLL in first CR received T-cell-depleted allogeneic marrow grafts from HLA/MLC-compatible related donors in this series. The product limit estimate of DFS in this group is 45% at 3 years (95% CI, 24% to 66%), and the survivors have been monitored for a median of 72 months. Seven of the 12 patients transplanted between the ages of 30 and 43 years survive free of disease. Graft rejection, a complication observed in other series using some form of T-cell–depleted marrow allografts,18,19,35 occurred in five of the 31 patients and thereby reduced overall survival and DFS. However, the probability of relapse was only 13% (95% CI, 1% to 25%), which compares favorably with relapse rates reported in similar series using unmodified BMT and in vivo pharmacologic prophylaxis against GvHD.7-10,34,35

Dinsmore et al35 first reported results from this institution that included 30 patients undergoing unmodified BMT as treatment for ANLL in first CR. Pediatric patients represented a significant subset of this group, although the median age was 20 years (range, 1 to 38). The probability of DFS at a median follow-up of 28 months was 55% ± 9.2%, with a relapse rate of 17.3%. However, among patients 20 years and older in first or second remission, the 3-year probability of DFS decreased to 31% ± 11.5%. Brochstein et al36 subsequently reported longer follow-up for these and additional patients less than 20 years of age undergoing conventional BMT for ANLL in first CR; their probability of DFS at 5 years was 66% ± 10%, with no relapses. In the original group that included adults, acute GvHD had a negative effect on survival, but no apparent influence on relapse35; the numbers of patients were too small to observe an effect of chronic GvHD.

Other institutions have reported similar DFS probabilities in adults prepared with combined cyclophosphamide and radiation- or busulfan-based regimens, who have received unmodified bone marrow allografts and posttransplant pharmacologic prophylaxis against GvHD. Early studies from City of Hope38 and UCLA37 in patients of similar age and disease status to those reported here, demonstrated DFS probabilities of 40% to 50% at approximately 4 years, with relapse rates between 8% and 40%. Data from the Seattle program yielded 3- to 5-year DFS probabilities of 40% to 50% in adult ANLL patients receiving conventional grafts in first remission; relapse rates varied between approximately 15% and 30%,7,34,38 Single-institution and multicenter trials using busulfan and cyclophosphamide cytoreduction in children and adults achieved 45% to 64% DFS and 13% to 14% relapse rates at 3 years following unmodified marrow transplants for ANLL in first CR.39,40 More effective posttransplant immune suppression reduced the incidence and severity of acute GvHD and its associated nonleukemic mortality. This resulted in improved DFS, although neither chronic GvHD (~50% to 45% incidence) nor the probability of remaining in remission was significantly altered.5,40 McGlave et al9 analyzed results of conventional transplants administered to 73 patients with ANLL in first CR, including 32 adults above the age of 18 years.
(mean, 28.6; range, 18 to 45). The 4-year probability of DFS was 60% ± 12%, with a relapse rate of 13% ± 10%. Age had no effect on outcome in this series. However, almost a quarter of the survivors experienced significant functional impairment secondary to the transplant procedure, and about half of these were as a direct sequela of GvHD.

Experimental animal models have conclusively established that mature T lymphocytes in the marrow allograft, rather than T-cell progeny of donor stem cells, are the effectors of GvHD. This is true across both major and minor histocompatibility barriers (the latter requiring class I MHC identity). One of the principal goals in using T-cell-depleted marrow allografts in human transplantation has therefore been to reduce the incidence and severity of GvHD and its complications. This would potentially allow older and/or partially mismatched patients of this therapy postremission. In this respect, T-cell–depleted BMT have been highly successful. Prentice et al prevented grade II to IV acute GvHD in leukemic patients receiving marrow allografts that were more than 99% depleted of T cells by two anti-CD3 monoclonal antibodies. Reiner et al similarly eliminated GvHD in infants with congenital immunodeficiencies who received haploidentical parental allografts depleted of T cells by lectin and sRBC rosetting. Neither of these trials administered posttransplant pharmacologic immunosuppression against GvHD. Seattle and UCLA reported results of T-cell–depleted marrow allografts in patients with a variety of hematologic malignancies, among which ANLL patients in first CR represented small subsets (15% or 25%, respectively). T-cell depletion was accomplished by monoclonal antibody and complement techniques. The patients in these latter two series also received pharmacologic prophylaxis against GvHD, which included cyclosporine in most regimens. Both groups significantly reduced the incidence and severity of acute GvHD, but at the expense of a 25% to 35% incidence of graft rejection. Compared with patients undergoing unmodified marrow transplants, no discernible differences were observed in leukemic relapse by the Seattle group. However, the UCLA study did identify more clinical and cytogenetic relapses among their patients who received T-cell–depleted allografts and posttransplant immunosuppression (four of seven patients with ANLL, first or second CR not specified for relapse). The two-step physical separation method we have used to modify marrow allografts at this institution achieves a 2.5- to 3-log depletion of clonable T cells and does not require additional immunosuppressive therapy posttransplant (although two of the 31 patients did receive ATG and steroids, nominally administered for rejection prophylaxis). This series, just as others using T-cell depletion, was plagued by immune-mediated graft failure. Although time to engraftment was not significantly different from that observed in recipients of unmodified grafts in our overall transplant series, five patients (15%) suffered immune-mediated graft failure between 15 and 52 days following T-cell–depleted BMT. However, only three of 26 engrafted patients developed acute GvHD (one patient, grade I; two patients, grade II), limited entirely to the skin. None of these three patients died of acute GvHD or its associated complications, and each case resolved after a brief course of systemic steroid therapy. None of the recipients of T-cell–depleted grafts have received any further exogenous immunosuppression. Also, there have been no cases of clinically apparent chronic GvHD, and all long-term survivors have a performance status of 100%. These results contrast with those of unmodified BMT, following which 30% to 70% of recipients of HLA/MLC-compatible marrow develop acute GvHD despite pharmacologic prophylaxis. Chronic GvHD also occurs in approximately 30% of patients surviving 100 days or longer following unmodified BMT, often with significant morbidity and functional impairment.

In a large early series of patients undergoing unmodified BMTs with pharmacologic GvHD prophylaxis, chronic GvHD was associated with improved remission rates. However, these were retrospective analyses that included patients at various stages of different hematologic neoplasms; also, only patients who were alive and disease-free at 150 days or more posttransplant could be evaluated. Subsequently, Clift et al reported that chronic GvHD decreased the risk of relapse in patients transplanted in the first remission of ANLL, although these patients had a 5-year probability of relapse of 25%. Allogeneic BMT has also been associated with a reduced incidence of leukemic relapse when compared with syngeneic marrow grafts.

These studies have been interpreted as evidence of an essential role for GvHD-inducing alloreactive T cells in the expression of the antileukemic properties of a marrow allograft. The mechanism(s) underlying this graft-versus-leukemia phenomenon are not clearly established. However, host-reactive allogeneic donor T lymphocytes mediating GvHD hypothetically exert antitumor cytotoxicity either directly or indirectly through recruitment of other important lymphocyte effectors.

Whether GvHD and graft-versus-leukemia effect represent the same, distinct, or overlapping entities remains controversial. In multivariate analyses, neither acute nor chronic GvHD has independently affected freedom from relapse of ANLL when patients were transplanted in first CR. Moreover, despite the shortcomings of registry data that employ retrospective analyses from multiple centers using various preparative regimens, two key points emerge from a recent International Bone Marrow Transplant Registry (IBMTR) report. First, in patients with ANLL in first CR, conventional allograft recipients without GvHD still had a significantly lower relapse rate than recipients of syngeneic grafts. Second, the antileukemic efficacy of an allograft for this particular malignancy and CR status was not significantly abrogated by T-cell depletion.

It is therefore not surprising that we have observed only a 13% (95% CI, 1% to 25%) cause-specific probability of relapse, despite a profound reduction in the incidence and severity of acute GvHD and the elimination of clinically apparent chronic GvHD. However, not all T-cell depletion methods are the same. Other approaches (e.g., monoclonal antibody/C') typically do not remove as many mature T lymphocyte effectors as the two-step physical separation method used here. The majority of patients undergoing T-cell–depleted BMT in other series have therefore
often received additional pharmacologic prophylaxis against GvHD, typically cyclosporine A. In this regard, it is notable that early recovery of NK/LAK cell activity in our overall group of T-cell–depleted graft recipients has been strongly associated with stable engraftment and also with freedom from relapse in patients with chronic myelogenous leukemia. This may further explain why an increased risk of leukemic relapse, purported to be a complication of T-cell-depleted grafts administered by other groups, has not been confirmed as an increased cause of treatment failure in our patients. The low incidence of relapse has also been documented in other patients similar to our own, who have received grafts depleted of T cells by a different technique, but who have also not been treated with cyclosporine A.

Other factors particular to this group of patients have probably also contributed to outcome. The cytoreductive regimen used to prepare our patients may be sufficiently myeloablative to ensure a low incidence of relapse irrespective of the dose of T cells administered or the incidence of GvHD observed. The majority of our patients also underwent consolidation therapy before transplant. Furthermore, an irradiated lectin-agglutinated fraction (SBA+, see Materials and Methods) was empirically administered just before the actual T-cell–depleted marrow allograft, in order to provide a source of radioresistant accessory cells and to bind any persistently circulating antileukocyte antibodies. Clonable T cells cannot be recovered from this fraction after this amount of γ-irradiation (4,000 cGy, 137Cs). Whether our results would differ without the administration of these irradiated cells has not been systematically evaluated.

With regard to other nonleukemic causes of treatment failure, the incidence of posttransplant infectious complications was less than that reported by other centers using T-cell–depleted grafts and certainly no greater than other series of unmodified grafts where infections occur in the context of GvHD. The ability to diagnose and treat certain of these infectious complications, particularly interstitial pneumonitis due to CMV, has improved dramatically in the past several years, irrespective of the type of transplant. Results in all series should begin to reflect the benefits of this therapy. Idiopathic or radiation-associated interstitial pneumonitis was also not observed, presumably due to the use of HFTBI with protective lung shielding after 900 cGy and the reduction or elimination of clinically apparent acute and chronic GvHD.

In comparison to allogeneic transplants, nonleukemic morbidity and mortality are typically reduced following autologous BMT for ANLL in first CR. DFS rates comparable to those reported here have been observed by other centers following autologous BMT, despite the fact that leukemic relapse is a more frequent cause of treatment failure. Direct comparisons between allogeneic and autologous transplantation results for ANLL in first CR from various centers are difficult because of time censoring and patient selection biases. However, any advantage of allogeneic over autologous BMT for ANLL in first CR has not been clearly established in a single-institution trial, where pretransplant chemotherapy and peritransplant supportive care are held constant. To this end, we have instituted such a trial, particularly to address the graft-versus-leukemia effect of two transplantation approaches where clinical GvHD has essentially been eliminated.

In conclusion, our results indicate that allogeneic BMTs depleted of T cells by the method used here can induce sustained DFS in adults with de novo ANLL in first CR at rates comparable to those achieved following unmodified HLA/MLC-compatible marrow grafts. The incidence of acute GvHD has been markedly reduced and clinically apparent chronic GvHD has been eliminated. All long-term survivors have 100% performance statuses without chronic immunosuppressive therapy. This has been achieved without an increase in fatal infections or leukemic relapse compared with unmodified BMT for this disease. The major limitation to the success of these transplants has been graft rejection. As improved methods for ensuring engraftment are used, such transplants should offer significant advantages, particularly to the older and/or partially mismatched patient. Long-term DFS can thus be achieved without clinically apparent or severe GvHD or the need for chronic immunosuppressive therapy.

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REFERENCES


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T-cell-depleted allogeneic bone marrow transplantation in adults with acute nonlymphocytic leukemia in first remission

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