Autologous Bone Marrow Transplantation for Patients With Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia Following MDS

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Intensive chemotherapy followed by autologous bone marrow transplantation (ABMT) may provide an alternative therapy for young patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia following MDS (sAML) lacking a suitable donor. We report the results for 79 patients with MDS/sAML transplanted with autologous marrow in first complete remission (CR). Within the total group of 79, a cohort of 55 patients for whom the duration of first CR was known was compared with a matched control group of 110 patients with de novo AML. The 2-year survival, disease-free survival (DFS), and relapse rates for the 79 patients transplanted in first CR were 39%, 34%, and 64%, respectively. The relapse risk was greater than 55% for all stages and all disease categories. Patients younger than 40 years had a significantly (P = .04) better DFS (39%) than patients older than 40 years (25%). The DFS at 2 years was 28% for the cohort of 55 patients transplanted for MDS/sAML and 51% for those transplanted for de novo AML (P < .025). Relapse rates were 69% for patients with MDS/sAML and 40% for those with de novo AML (P = .007). ABMT for MDS or secondary leukemia results in a lower DFS when compared with similarly treated patients with de novo AML due to a higher relapse rate. The DFS of 28% for these patients suggests that autotransplantation may be a valuable therapy for this disease. The low treatment-related mortality rate of less than 10% supports the view that sufficient numbers of hematopoietic stem cells are present in patients with MDS to allow adequate repopulation after autologous stem-cell transplantation.

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MATERIALS AND METHODS

Data were retrieved from the registries of the Chronic and Acute Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. These registries continuously collect data related to patients transplanted by member teams. Reports were available for 114 patients from 41 centers. Seventy-nine of these patients were transplanted in first CR: 19 for RAEB or RAEBt, 39 for secondary leukemia, and 21 for MDS or secondary leukemia due to previous cytotoxic therapy. The median age for the 79 patients was 39 years (range, 0 to 63). Forty-five of 79 patients were aged less than 40 at the time of transplant (Table 1). The median interval between diagnosis and BMT was 9 months (range, 2 to 42) for 19 patients with MDS and 7 months (range, 3 to 23) for patients with that of 110 patients transplanted in first CR for de novo AML.

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transplanted for sAML or therapy-related MDS/AML. Cytogenetic data were only available for 18 patients. Seventy-three patients received bone marrow only, three patients were treated with collected peripheral stem cells, and three patients received both. None of the stem-cell grafts was subjected to purging procedures.

For the matched case-control analysis, we selected 55 patients with MDS or secondary leukemia for whom information was available on the interval from CR to transplant, and compared them with 110 patients treated by ABMT in first CR for de novo AML, and reported to the Acute Leukemia Working Party Registry. This registry contains data on approximately 1,000 patients treated in this way. Patients were matched for age (<40 v 40 years), interval from CR to transplant, and year of transplant.

**Definitions.** The classification of MDS and AML was performed according to the criteria of the French-American-British (FAB) working group. AML that develops after antecedent MDS with a duration of at least 3 months is defined as sAML (secondary leukemia). MDS or AML occurring after chemotherapy or radiotherapy is defined as therapy-related MDS or AML.

CR is defined as a normocellular marrow with less than 5% blast cells, including monocytoid cells, and less than 10% blast cells and promyelocytes. Peripheral blood counts should be in the normal range.

**Statistics.** The intervals for survival, DFS, relapse rate, and risk of transplant-related mortality were calculated from BMT. Relapsed patients were censored for transplant-related mortality from time of relapse. The prognostic value of covariables was studied by Kaplan-Meier curves and the log-rank test. The matched control study was analyzed with the stratified log-rank test.

**RESULTS**

Seventy-nine patients transplanted in first CR were assessable (Table 1). Thirty-two patients (41%) are alive and disease-free. The median follow-up duration of 36 surviving patients was 10 months (range, 0 to 89 months) and 12 months (range, 0 to 89) for patients remaining in CR. Only seven patients died as a consequence of treatment and 36 as a result of disease recurrence. Forty patients relapsed (51%). Fifteen patients are disease-free survivors more than 2 years therapy is a difficult issue. Patients who are not eligible for allogeneic BMT could be treated with postremission chemotherapy. Some patients may achieve prolonged DFS with this approach, but the overall median remission duration was usually less than 12 months. Patients without cytogenetic abnormalities appeared to have a better outcome after
Table 2. Actuarial 2-Year Survival, DFS, Relapse Rate, and Transplant-Related Mortality of 79 Patients Transplanted in First CR With ABMT

<table>
<thead>
<tr>
<th>Disease category</th>
<th>N</th>
<th>Survival</th>
<th>DFS</th>
<th>Relapse</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>19</td>
<td>46%</td>
<td>40%</td>
<td>58%</td>
<td>5%</td>
</tr>
<tr>
<td>sAML</td>
<td>39</td>
<td>34%</td>
<td>.68*</td>
<td>30%</td>
<td>.61*</td>
</tr>
<tr>
<td>Postcytotoxic MDS or sAML</td>
<td>21</td>
<td>41%</td>
<td>36%</td>
<td>60%</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>N</th>
<th>Survival</th>
<th>DFS</th>
<th>Relapse</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>45</td>
<td>46%</td>
<td>.09*</td>
<td>39%</td>
<td>.04*</td>
</tr>
<tr>
<td>≥40</td>
<td>34</td>
<td>27%</td>
<td>25%</td>
<td>72%</td>
<td>.05*</td>
</tr>
</tbody>
</table>

Abbreviation: TRM, treatment-related mortality.
* P value, log-rank test.

The experience with ABMT in patients with MDS or leukemia secondary to MDS is limited and the literature contains only case reports. From a large series of 82 adult patients with AML, six patients with a known preceding myelodysplastic state received ABMT in first remission. Three patients relapsed after transplant, and the overall leukemia-free survival was worse than that of the group without an antecedent hematologic disorder. A preliminary analysis from the European Group for Blood and Marrow Transplantation reported the results of ABMT in 17 patients with MDS. Engraftment occurred in 15 of 16 assessable patients. The median relapse-free survival duration was 11 months. Transplant-related mortality and death due to regeneration failure did not appear to occur more often than after ABMT for de novo AML. Hematopoietic engraftment was slow despite the sufficient number of colony-forming units—granulocyte, macrophage (CFU-GM) being collected per kilogram body weight ($5 \times 10^4$ kg). Laporte et al reported the results of ABMT with mafosfamide-treated marrow in patients with AML following MDS. The hematopoietic en-

Table 3. Comparison of MDS/sAML Study Group With Matched Control Group of Patients With De Novo AML

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>55</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>28</td>
</tr>
<tr>
<td>≥40</td>
<td>27</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
</tr>
<tr>
<td>Year of transplant</td>
<td></td>
</tr>
<tr>
<td>83-87</td>
<td>8</td>
</tr>
<tr>
<td>88-90</td>
<td>20</td>
</tr>
<tr>
<td>91-94</td>
<td>27</td>
</tr>
<tr>
<td>Interval, first CR to transplantation (mo)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>0-20</td>
</tr>
<tr>
<td>Alive (%)</td>
<td>20 (36)</td>
</tr>
<tr>
<td>Relapse-free alive (%)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Relapse (%)</td>
<td>31 (56)</td>
</tr>
<tr>
<td>Dead (%)</td>
<td>35 (64)</td>
</tr>
<tr>
<td>Treatment-related death (%)</td>
<td>6 (11)</td>
</tr>
</tbody>
</table>

Fig 1. (A) Actuarial survival, (B) leukemia-free survival (LFS), and (C) relapse risk of 55 patients transplanted in first CR for MDS, sAML, or therapy-related MDS/leukemia compared with 110 matched patients transplanted in first CR for de novo AML. MDS refers to myelodysplastic syndromes, secondary AML, and therapy related MDS/AML; AML refers to de novo AML.
graftment was also slow in these seven patients, but all pa-
tients engrafted except for one who died of treatment-related
causes before engrafting.

MDSs are clonal stem-cell disorders. This may raise con-
cern about the presence of sufficient numbers of residual
normal stem cells to perform autologous stem-cell trans-
plantation. However, chemotherapy is capable to induce a
cytogenetically normal CR in patients with a cytogenetic
marker of the malignant clone. Seven of eight patients with
cytogenetic abnormalities in CR after chemotherapy ap-
peared to have a cytogenetically normal bone marrow.1 In
addition, polymerase chain reaction techniques based on X-
chromosome inactivation patterns demonstrated polyclon-
ality in the peripheral stem-cell harvests of three patients
with MDS.23 In this retrospective analysis from the European
Group for Blood and Marrow Transplantation registries, only
seven of 79 patients transplanted in first CR died due to
complications of the transplant. Moreover, the transplant-
related mortality was not higher than the transplant-related
mortality of the matched control group of patients trans-
planted for de novo AML in first CR. This would suggest
that the engraftment capabilities of stem cells derived from
patients with MDS are usually sufficient to restore hemato-
poiesis to levels that prevent fatal infectious and hemorrhagic
complications. The administration of a higher number of
stem cells, obtained by mobilization of the stem cells into
the peripheral blood, may improve the speed of engraftment.
Pilot studies showed the feasibility of collecting peripheral
stem cells in patients in CR of MDS or sAML.24,25 The engraftment appeared to be much faster, but this approach
is not likely to improve substantially the treatment-related
mortality of autologous transplantation in MDS, since the
mortality is already less than 10% after the use of autologous
bone marrow stem cells.

The main reason for treatment failure was a high relapse
risk after the autologous stem-cell procedure. The relapse
risk was higher than 55% for all stages and all disease cate-
gories. Late relapses beyond 2 years were rare events, al-
though only 15 patients were at risk beyond this time.
Age less than 40 years at the time of transplant was associated
with a significantly better prognosis, with a DFS of 39%,
mainly due to a lower relapse risk in the younger age group.
The lower relapse risk in the younger age group may be due
to several factors, such as the duration of disease before
treatment and the absence of cytogenetic abnormalities,
which are associated with a poor outcome. The limited num-
ber of patients in the present study and the lack of cytoge-
netic data precluded an analysis on cytogenetic prognostic
criteria. A recently completed joint study of the Leukemia
Co-operative Group of the European Organization for Treat-
ment and Research in Cancer and the European Group for
Blood and Marrow Transplantation evaluated prospectively
the role of autologous stem-cell transplantation in 185 pa-
tients with MDS and secondary leukemia.24 Preliminary re-
sults showed that cytogenetic characteristics had a major
impact on treatment outcome. The actuarial 2-year survival
of patients with good risk or intermediate risk was 52%
versus 28% in the poor-risk group.24

ABMT for MDS and secondary leukemia resulted in a
lower DFS than ABMT for de novo AML. This difference
was mainly due to a higher relapse rate in the MDS/sAML
group, since the mortality rate was low in both patient
groups. The higher relapse rate in patients treated for MDS
or secondary leukemia suggests a higher burden of residual
disease in these patients. For that reason, it is important to
monitor carefully residual disease in future studies both by
cytogenetic techniques and by molecular techniques.

ABMT in first CR may be the treatment of choice for
patients with MDS or sAML if a histocompatible sibling
donor is lacking. Allogeneic BMT with a matched unrelated
donor is associated with a substantially higher treatment-
related mortality. Anderson et al26 described the results of 52
patients with MDS and sAML transplanted with an unrelated
donor. The 2-year DFS, relapse, and nonrelapse mortality
rates were 38%, 28%, and 48%, respectively. The incidence
of the nonrelapse mortality was higher compared with HLA-
identical related recipients. Increasing age was significantly
associated with increased risk of death from nonrelapse
causes. The nonrelapse mortality was 16% in patients
younger than 20 years, 66% and in patients between 21 and
40 years, and 53% in patients older than 40 years.26 A
substantial number of patients may not reach the autologous
stem-cell transplant procedure due to failure to induce remis-
ion or failure to collect sufficient number of stem cells.
Careful clinical evaluation of the prognostic factors, such as
age, chance to achieve CR, and availability of a matched
unrelated donor, should guide the treating physician in advis-
ing the patient of the available treatment options. Further
analyses and prospective studies may identify patients with
MDS who will benefit from intensive antileukemic therapy
followed by autologous stem-cell transplantation.

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