ACUTE MYELOGENOUS LEUKEMIAS (AMLs) and myelodysplastic syndromes (MDSs) are considered to differ with regard to response rate and remission duration after chemotherapy. Patients suffering from AML can be cured by conventional chemotherapy whereas those with MDS are considered incurable.

Therapy for MDS using low-dose cytostatic agents, growth factors, or substances aimed at differentiation induction is capable of prolonging survival and improving quality of life. Long-term benefit, however, can only be achieved by eradication of the abnormal clone and restoration of normal hematopoiesis. Whether this can be accomplished using intensive chemotherapy or the transplantation of hematopoietic stem cells is discussed in this article.

AML-TYPE CHEMOTHERAPY FOR MDS

Treatment of MDSs with AML-type chemotherapeutic regimens is capable of inducing complete remission (CR). This was shown in the early 1980s by Armitage et al and Mertelsmann et al who reported CR rates of 15% and 45%, respectively. Later, these data were confirmed by other groups using various combinations of cytostatic agents.

Most groups have used daunorubicin combined with conventional or high-dose cytosine arabinoside (Ara-C) or regimens adding thioguanine. Furthermore, combinations of ARA-C plus idarubicin, mitoxantrone plus etoposide, fludarabine plus ARA-C, or ARA-C, idarubicin plus etoposide have been tested. Results are summarized in Tables 1 through 3. CR rates vary widely, ranging from 15% attained by Kantarjian et al in 26 patients with myelodysplasia after previous cytotoxic therapy, to 61% reported by Michels et al in 31 patients with refractory anemia with excess of blasts in transformation (RAEB-t) without previous exposure to leukemogenic chemicals. In smaller series, remission rates of up to 100% (6 CRs in 6 RAEB-t cases) have been reported.

On average, CR rates of patients with MDS appear lower than those of patients with de novo AML treated with either similar or identical chemotherapeutic regimens. This impression is supported by Fenaux et al, who reached CR rates of 71% in de novo AML and 48% in de novo MDS with an identical treatment protocol. However, the higher median age of MDS patients compared with AML patients may be at least partly responsible for the differences observed. In patients younger than 45 years, De Witte et al obtained CR rates of 75% for de novo AML and 71% for MDS with an identical treatment protocol. Whether the CR rate is different in MDS and AML may also depend on details of the treatment protocol used.

Reasons for the lower remission rates in MDS observed in some studies were (1) drug resistance of the neoplastic cell clone and (2) longer duration of the aplasia resulting in a higher early death rate. De Witte et al, Richard et al, and Fenaux et al have reported a longer duration of the pancytopenic period after completion of chemotherapy, resulting in toxic death rates of 14%, 22%, and 21%, respectively. However, Tricot et al, Hoffmann et al, and Aul and Schneider failed to confirm a prolonged pancytopenic period in MDS patients treated aggressively.

In almost every instance, achievement of a CR is followed by complete hematologic recovery and restoration of polyclonal hematopoiesis. However, duration of remission usually is short (Tables 1 through 3). Median remission duration is less than 12 months, and remissions exceeding 24 months are the exceptions to the rule. Overall survival rates were reported to be 8% at 4 years after therapy at the Memorial Sloan-Kettering Cancer Center (MSKCC) and
Table 1. Results of Intensive Chemotherapy for Nonspecified Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>References</th>
<th>Induction Therapy</th>
<th>Patients</th>
<th>CR</th>
<th>Early Deaths</th>
<th>No Remission</th>
<th>Remission Duration (mo)</th>
<th>Median Age (Range)</th>
<th>Secondary MDS</th>
<th>Previous Low-Dose ARA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Witte16</td>
<td>AML</td>
<td>14</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>4 × BMT, 6 relapses (4-11 mo)</td>
<td>42 (27 to 58)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fenaux26</td>
<td>AML</td>
<td>31</td>
<td>17</td>
<td>—</td>
<td>—</td>
<td>Median 9 months</td>
<td>54 (18 to 68)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Richard57</td>
<td>High-dose ARA-C</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>66</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mertelsmann57</td>
<td>AML</td>
<td>31</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>8% survival/4 yrs</td>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kantarjian57</td>
<td>AML</td>
<td>26*</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>26</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Michels48,49</td>
<td>AML</td>
<td>8</td>
<td>3</td>
<td>—</td>
<td>5</td>
<td>—</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LeBeau43</td>
<td>TAD</td>
<td>2</td>
<td>0</td>
<td>—</td>
<td>2</td>
<td>68, 74</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aul7</td>
<td>AML</td>
<td>76</td>
<td>48</td>
<td>11</td>
<td>17</td>
<td>23% disease-free survival/5 years</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Low-dose ARA-C was given to 12 of 112 patients.
Abbreviations: TAD, thioguanine, ARA-C, anthracycline; AML, various AML type chemotherapeutic regimens.

7% after 3 years in the report by De Witte et al.16 The relapse-free survival rate was 25% and 0% in patients with normal or abnormal karyotypes, respectively, in the report of Fenaux et al.24-26

THE FRENCH-AMERICAN BRITISH CATEGORIES OF THE MDSs

Because the MDSs comprise an extremely heterogeneous group of disorders, the question arises whether response rates after aggressive chemotherapy are different for the various types of MDS. At present, this question cannot be adequately answered because of the scarcity of data on results of chemotherapy in refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), and chronic myelomonocytic leukemia (CMML). Almost all data on chemotherapy for MDS have been obtained in patients suffering from RAEB and RAEB-t. For these two categories results of aggressive therapy are given in Tables 2 and 3.

For CMML only the MSKCC47 and the M.D. Anderson Cancer Center in Houston22 have published data on a relevant number of cases. They obtained 9 CRs in 14 patients (MSKCC) and two CRs in seven patients (M.D. Anderson) treated aggressively. Data on peripheral blood leukocyte counts in those patients are lacking. Whether the patients represented CMML cases of myeloproliferative or myelodysplastic nature has not been stated.11,65

For RA and RARS, some case reports have been published. Estey et al22 have achieved CRs in six of nine patients treated with fludarabine administered in combination with ARA-C plus granulocyte colony-stimulating factor (G-CSF) in five patients.

Overall, treatment outcome is rather poor for any MDS category compared with data obtained in AML. However, the question arises if this difference still exists when prognostically favorable cases of AML characterized by inversion 16, translocation 8;21 or translocation 15;17

Table 2. Results of Intensive Chemotherapy for RAEB

<table>
<thead>
<tr>
<th>References</th>
<th>Induction Therapy</th>
<th>No. of Patients</th>
<th>CR</th>
<th>Early Deaths</th>
<th>No Remission</th>
<th>Remission Duration (mo)</th>
<th>Median Age (Range)</th>
<th>Secondary MDS</th>
<th>Previous Low-Dose ARA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenaux24</td>
<td>Rubidazonne</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2+</td>
<td>39, 58</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Richard57</td>
<td>High-dose ARA-C</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>—</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tricot63</td>
<td>AD, high-dose ARA-C</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>8, 13 + BMT</td>
<td>4, 24, 28</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

AD, ARA-C, daunorubicin.
Table 3. Results of Intensive Chemotherapy for RAEB-t

<table>
<thead>
<tr>
<th>References</th>
<th>Induction Therapy</th>
<th>No. Patients</th>
<th>CR</th>
<th>Early Deaths</th>
<th>No. Remission</th>
<th>Remission Duration (mo)</th>
<th>Median Age (Range)</th>
<th>Secondary MDS</th>
<th>Previous Low-Dose ARA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aul &amp; Fenaux</td>
<td>TAD</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>223+, 5, 29, 36+</td>
<td>52 (17 to 57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fenaux</td>
<td>RA</td>
<td>16</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>1+, 2, 4, 5, 5, 9+, 13, 25+</td>
<td>47 (18 to 65)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Richard</td>
<td>High-dose ARA-C</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>69</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Michels</td>
<td>AML</td>
<td>31</td>
<td>19</td>
<td>—</td>
<td>12</td>
<td>14 relapses</td>
<td>44 (?)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tricot</td>
<td>High-dose ARA-C</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>11, 12, 12</td>
<td>64 (40 to 78)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Scoazec</td>
<td>AML</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>11, 24, 27, 32</td>
<td>27 (18 to 56)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Armitage</td>
<td>AML</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>37+</td>
<td>34, 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estey</td>
<td>FLA(G)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>37+</td>
<td>34, 38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TAD, thioguanine, ARA-C, anthracycline; RA, rubidazone; AML, various AML type chemotherapeutic regimens; FLA(G), fludarabine, ARA-C, plus or minus G-CSF.

are excluded. For AML patients remaining after exclusion of these categories, long-term event-free survival is less than 20%.

PROGNOSTIC FACTORS IN CHEMOTHERAPY FOR MDS

In view of the divergent results of aggressive therapy for MDS, prognostic factors for response to intensive chemotherapy must be identified. Patient age less than 45 to 50 years is a well-established prognostic factor after aggressive therapy for MDS, as shown by Armitage et al, Tricot and Boogaerts (less than 50 years, 86% CR; greater than 50 years, 25% CR), Michels et al (less than 45 years, 77% CR; greater than 45 years, 43% CR), and Gajewski et al. (less than 47 years, 77% CR; greater than 47 years, 58% CR).

Reports on aggressive chemotherapy in MDS, as shown in Tables 1 through 3, are almost entirely restricted to de novo cases. Thus, a direct comparison of treatment outcome in de novo and secondary cases of MDS is impossible. In secondary MDS, Kantarjian et al obtained a CR rate of 15% with AML-type chemotherapeutic regimens, and Michels et al obtained three CRs in eight patients. Overall, these data as well as the scarcity of data on therapy in secondary cases of MDS do suggest that a prior exposure to leukemogenic cytotoxic agents is a poor prognostic factor for success of aggressive chemotherapy in MDS.

Cytogenetic analysis has become an increasingly recognized tool in the primary diagnosis of hematologic malignancies. The importance of this technique is underlined by the data of Fenaux et al, who obtained CRs in 57% of MDS patients with normal karyotypes, contrasting with 31% CRs in 13 patients with rearrangements or monosomies of chromosomes 5 and/or 7, and three CRs in six patients with other single chromosomal rearrangements. CRs of patients with abnormal karyotypes were extremely unstable, with patients relapsing within 5 months. In contrast, 25% of the patients without cytogenetic abnormalities remained relapse-free 3 years after therapy. Similar data on the prognostic significance of aberrations of chromosomes 5 and 7 in aggressively treated patients have been provided by Fenaux et al as well as by the M.D. Anderson group in 72 patients with therapy-related MDS and AML (4 of 31 CRs versus 7 of 13 CRs in patients with normal karyotypes). De Witte et al and Tricot and Boogaerts, however, did not observe differences in remission rates relative to the presence or absence of chromosomal aberrations. The presence of Auer rods may imply a better prognosis.

CHEMOTHERAPY AFTER CONVERSION TO ACUTE LEUKEMIA

More than 50% of the patients suffering from MDS experience progression of the disease to frank leukemia. In view of the poor results of therapy in the myelodysplastic phase, the question is whether one should withhold antileukemic therapy until progression to frank leukemia. Table 4 gives an overview on results of aggressive therapy for AML after a preceding myelo-
CHEMOTHERAPY AND BMT

Table 4. Results of Intensive Chemotherapy for AML after a Preceding MDS

<table>
<thead>
<tr>
<th>References</th>
<th>Induction Therapy</th>
<th>No. of Patients</th>
<th>CR</th>
<th>Early Deaths</th>
<th>No Remission</th>
<th>Remission Duration (mo)</th>
<th>Median Age (Range)</th>
<th>Secondary AML</th>
<th>Previous Low-Dose ARA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aul8'9</td>
<td>TAD</td>
<td>13</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>9, 1+, 5, 4+, 23, 5</td>
<td>55 (32 to 65)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Fenaux24</td>
<td>RA</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>6, 11+, 14, 42+</td>
<td>55 (23 to 68)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fenaux25</td>
<td>RA</td>
<td>16</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>Median 10 months</td>
<td>54 (18 to 68)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>De Witte16</td>
<td>AML</td>
<td>15*</td>
<td>13</td>
<td>2</td>
<td>7</td>
<td>11 relapses (2 to 25 mo)</td>
<td>47 (26 to 65)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Mertelsmann97</td>
<td>AML</td>
<td>16</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>56 (0 to 0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Keating36</td>
<td>ROAP</td>
<td>32</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>56 (0 to 0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Preisler54,35</td>
<td>High-dose ARA-C</td>
<td>11</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>More than 50 years</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pedersen-Bjer-</td>
<td>AML</td>
<td>3</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>gaard93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gajewski28</td>
<td>TAD</td>
<td>44</td>
<td>18</td>
<td>9</td>
<td>17</td>
<td>17% DSF/3 years</td>
<td>59 (18 to 76)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Richard57</td>
<td>AML</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2, 9, 10, 12, 15+, 19</td>
<td>59 (32 to 71)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tricot53</td>
<td>High-dose ARA-C</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>BMT, BMT</td>
<td>27, 34, 67</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tallman52</td>
<td>AML</td>
<td>10</td>
<td>2</td>
<td>—</td>
<td>3</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hoyle38</td>
<td>TAD</td>
<td>36</td>
<td>15</td>
<td>9</td>
<td>12</td>
<td>2+, 2+, 4, 4, 5, 5, 5, 5, 8+, 9, 35+, 21, 15+, 13+, 19+, 20+</td>
<td>61 (18 to 79)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Knauf60</td>
<td>NOVE</td>
<td>21</td>
<td>12</td>
<td>2</td>
<td>8</td>
<td>7 (2 to 10 mo)</td>
<td>56 (28 to 67)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>LeBeau43</td>
<td>AML</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>57+</td>
<td>51 (28 to 67)</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

*5 patients with MDS, but after chemotherapy.

Abbreviations: TAD, thioguanine, ARA-C, anthracycline; RA, rubidazone, ARA-C; AML, various AML type chemotherapeutic regimens; ROAP, rubidazone, ARA-C, vincristine, prednisone; NOVE, mitoxantrone and etoposide; DSF, disease-free survival.

dysplastic syndrome. The CR rate of the studies summarized in Table 4 is 37% in 231 patients. As can be derived from the table, some groups have treated patients in either phase of the disease and have received lower CR rates and poorer long-term results in those patients in whom treatment was started after conversion of the disease to overt leukemia.

TRANSPLANTATION OF HEMATOPOIETIC CELLS

Allogeneic Bone Marrow Transplantation

Given the poor results of other treatment modalities with curative potential, allogeneic bone marrow transplantation (BMT) is the treatment of choice for younger patients with MDS who are lucky enough to have a histocompatible sibling donor. The first cases of successful marrow transplants in MDS patients have been reported more than 10 years ago.4,12,15,32 Meanwhile, several larger BMT series of adult patients from single centers or registries have been published.1,2,3,5,20,45,46,50,51,56,61,64 Table 5 summarizes studies that encompass results of allogeneic BMT in 20 or more patients with MDS. Transplant data for children with MDS are still relatively scarce10,14,31 reflecting the fact that MDS in children is rare.33

The results of treatment with allogeneic BMT vary considerably depending on the subtype of disease at the time of transplantation and various other clinical factors such as the presence of cytogenetic abnormalities,20,46 age,1,2 and the percentage of blasts in the bone marrow at the time of transplantation.1,2,51 For that reason, different disease categories and their influence on treatment outcome after BMT are discussed below; other factors found to be of significant importance in the major studies are listed in Table 5.

RA and RARS

Patients with RA and RARS are generally considered good candidates for BMT. Transplant-related mortality is relatively low, relapses of the underlying disease are surprisingly rare, and disease-free survival usually exceeds 50%.1,2,20 Patients with RA and RARS as well as
those with a clinical picture of severe aplastic anemia but with cytogenetic aberrations typically associated with MDS (such as monosomy 7) must be prepared with an aggressive marrow-ablative regimen. A conditioning regimen consisting of cyclophosphamide alone is not sufficient to eradicate the malignant clone. Such patients are at high risk to experience persisting or rapidly reemerging disease. Because of the relatively low number of patients transplanted with RA and RARS, it is still impossible to assess the impact of most pretransplant vari-

<table>
<thead>
<tr>
<th>References</th>
<th>No. of Patients</th>
<th>Median Age (Yr)</th>
<th>Degree of Histocompatibility (No. of Patients)</th>
<th>Disease Subtype</th>
<th>Pre-BMT Regimen (No. of Patients)</th>
<th>Treatment-Related Deaths</th>
<th>No. of Relapses</th>
<th>Disease-Free Survival</th>
<th>Prognostic Factor(s) for Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marmont et al.</td>
<td>123</td>
<td>0 to 9 (7)</td>
<td>ID all (18)</td>
<td>RAEB</td>
<td>TBI + CHEMO (92)</td>
<td>nm</td>
<td>[34 ± 18]% at 2 yrs</td>
<td>[33 ± 11]% at 2 yrs</td>
<td>-chromosomal abnormalities</td>
</tr>
<tr>
<td>Anderson</td>
<td>93</td>
<td>30 (range, 10 to 60)</td>
<td>ID 84 (RAES)</td>
<td>TBI + CHEMO (88)</td>
<td>CY + BUS + CY (5)</td>
<td>37 (40%) at 5 yrs</td>
<td>18 (19%)</td>
<td>36 pts (41%) median 6.1 yrs at 5 yrs</td>
<td>-younger age shorter disease duration</td>
</tr>
<tr>
<td>Sutton et al.</td>
<td>86</td>
<td>35 (range, 9 to 55)</td>
<td>ID 84 (sAML)</td>
<td>TBI + CHEMO (53)</td>
<td>30 (35%) at 23% 30 (23%)</td>
<td>20 (23%)</td>
<td>33 pts (38%) medium 28 mos (35.2%) at 30 mos</td>
<td>+RA, RAEB, RAEB-t with stable disease</td>
<td>-untreated disease for RAEB-t sAML ony</td>
</tr>
<tr>
<td>De Witte et al.</td>
<td>78</td>
<td>32</td>
<td>ID 74 (RAEB)</td>
<td>TBI + CHEMO (69)</td>
<td>25 (32%) at 18 (23%)</td>
<td>35 pts (45%) 2-91 mos 2 (RA 68%) [RAEB 74% [RAEB 60%]</td>
<td>+CR after intensive chemotherapy for sAML, RA, RAEB, RAEB-t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uberti et al.</td>
<td>32</td>
<td>33</td>
<td>ID 21 (RAEB)</td>
<td>TBI + CHEMO (9)</td>
<td>13 (39%) at 2 (6%)</td>
<td>19 pts (56%) median 24 mos (52%)</td>
<td>Non-ID marrow donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navilli et al.</td>
<td>23</td>
<td>35 (range, 18 to 55)</td>
<td>ID 22 (RAEB)</td>
<td>TBI + CHEMO (22)</td>
<td>10 (43%) at 5 (22%)</td>
<td>8 pts (35%) median 27 mos (35%) at 3 yrs</td>
<td>Younger age</td>
<td></td>
<td></td>
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<tr>
<td>Longmore et al.</td>
<td>23</td>
<td>23</td>
<td>ID 21 (RAEB)</td>
<td>TBI + CHEMO (13)</td>
<td>9 (39%) at 4 (17%)</td>
<td>10 pts (43%) [Primary MDS 66% [BMDS/sAML 27%]</td>
<td>T-cell depletion plus marrow fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Donnell et al.</td>
<td>20</td>
<td>36</td>
<td>ID 19 (RAEB)</td>
<td>TBI + CHEMO (3)</td>
<td>9 (45%) at 4 (20%)</td>
<td>7 pts (35%) (1 additional pt disease-free &gt; 1 year after second BMT)</td>
<td>&gt;10% blasts in BM</td>
<td></td>
<td></td>
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</tbody>
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Abbreviations: BMT, bone marrow transplant; ID, genotypically identical sibling donor; twin, identical twin; MM, family donor mismatched for 1-3 antigens; MUD, matched or partially mismatched unrelated donor; RA, refractory anemia; RAEB-t, RA with excess of blasts (in transformation); CMMML, chronic myelomonocytic leukemia; sAML, AML developing from prior MDS or AML; NIM = not mentioned; TBI, total body irradiation; FTBI, fractionated total body irradiation; CHEMO, chemotherapy; BUS, busulfan; CY, cyclophosphamide; CVB, CY, VP-16, BCNU; FA, Fanconi's anemia.

Product limit estimate for BMT-related deaths.
Product limit estimate of relapse.
Product limit estimate of disease-free survival.
An additional patient grafted for RA and Hodgkin's disease relapsed with Hodgkin's disease.
ables on the outcome of BMT. A multivariate analysis from Seattle showed that disease duration did not significantly influence overall or disease-free survival; however, transplant-related complications were lower in patients transplanted early in the course of disease. Therefore, early transplantation—possibly within the first year after diagnosis—seems justified: this practice might help patients to avoid transplant-related complications resulting from iron overload or opportunistic infections contracted during prolonged periods of pancytopenia.

**RAEB and RAEB-t**

Outcome of BMT in patients with RAEB or RAEB-t is less favorable than that found in patients with RA(RS). The main reason for this difference is a substantially higher relapse rate. The disease-free survival curves are significantly lower than in patients with RARS. An early European Group for Blood and Marrow Transplantation (EBMT) analysis had shown an actuarial disease-free survival of 74% for patients transplanted with RAEB and of 50% when the patient had RAEB-t. A later analysis showed a 3-year disease-free survival of 32% in 18 patients transplanted for RAEB and 27% in 11 patients transplanted for RAEB-t. Late relapses occurred especially in patients with RAEB showing a relapse pattern that was similar to that of chronic myeloid leukemia after BMT. The actuarial relapse rate at 3 years in this particular group of patients was higher than 50%. One of the recent analyses from Seattle showed a comparable cumulative relapse risk of 49% in 47 patients transplanted with excess of blasts. Half the relapses occurred more than 1 year after BMT. Nevertheless, immediate BMT is the only therapeutic option with a chance of cure and patients should be encouraged to proceed to BMT as soon as possible.

**CMML**

Only a few patients with CMML have been treated with BMT. Again, allogeneic BMT is the only treatment modality offering a chance of cure to such patients; it must be stressed, however, that because of the scarcity of data comments on the probability of disease-free survival, relapse rate, and transplant-related mortality after BMT for CMML seem premature.

**Secondary AML**

Most European transplant centers will consider BMT for secondary AML (sAML) only after remission induction chemotherapy has been administered. This approach, however, has never been formally tested. The results of BMT as primary therapy appeared worse for patients with overt sAML as compared with those with RAEB-t. Prolonged disease-free survival can be expected in approximately 20% of patients transplanted for sAML. Some patients with hypocellular marrow who are particularly unlikely to respond favorably to intensive chemotherapy have achieved prolonged disease-free survival after BMT without preceding chemotherapy. Therefore, immediate BMT should be considered for each patient with sAML whose poor general condition or problems associated with low blood counts (fever and bleeding tendency) do not preclude this approach.

Remission duration for patients treated with AML-type remission induction chemotherapy usually is short, especially if cytogenetic abnormalities were present at the time of diagnosis. Accordingly, BMT should be offered to such patients immediately after a complete or even a partial remission has been achieved by intensive chemotherapy. The 2-year disease-free survival in 16 patients transplanted in CR after chemotherapy was 60%. Patients with a partial response to intensive chemotherapy responded less well and showed a 2-year disease-free survival of 18% whereas none of those who either relapsed or were resistant to chemotherapy survived BMT for 2 years or more.

**Therapy-related MDS and AML**

The actuarial disease-free survival of 11 patients transplanted for therapy-related MDS/AML was 27% compared with 56% for 12 patients who were transplanted for primary MDS. However, the two groups were not completely comparable because the number of patients with overt AML was five in the therapy-related group as compared with none in the group with primary MDS. All seven patients transplanted for overt AML secondary to
Hodgkin's disease died of multiorgan failure (four patients) or leukemia. Four patients with AML secondary to treatment for Hodgkin's disease were transplanted in first CR. Two patients were alive and disease-free at the time of writing. The EBMT compared transplant results of 28 patients with therapy-related RAEB-t or AML with the results of 53 patients with de novo RAEB-t or AML evolved from MDS. The overall disease-free survival was identical, but the relapse rate was slightly higher in the therapy-related group.

Alternative Sources of Hematopoietic Stem Cells

Transplants from unrelated marrow donors. Unfortunately, at least two thirds of patients young enough to be candidates for an allogeneic BMT lack a human leukocyte antigen (HLA)-identical sibling donor. For some of these patients, a partially matched family donor can be identified. With the growing number of volunteer donors registered worldwide, allogeneic BMT from a closely or fully matched unrelated donor has become another realistic alternative. Although a probability of disease-free survival of 18 ± 14% at 2 years reported by Kernan et al for 32 patients grafted from unrelated donors was somewhat disappointing recent data on unrelated BMTs in children are more encouraging. Casper et al reported that five of nine patients survived 27 to 80 months posttransplant with four of them staying in remission. An analysis of unrelated donor BMTs in children performed in Seattle included five children with MDS, three of whom relapsed, one patient died of transplant-related causes, and one patient was disease-free at the time of publication.

Autologous BMT. One-hundred fourteen recipients of autologous marrow grafts who suffered from MDS or AML secondary to MDS have been reported to the EBMT. The overall survival at 2 years of the 79 patients transplanted in first CR was 39%, disease-free survival was 34%, the actuarial relapse rate was 64%. Nineteen patients were transplanted for MDS which had not progressed to AML before autologous BMT. The actuarial disease-free survival at 2 years in these patients was 40% and the relapse rate 58%. Thirty-nine MDS patients had progressed to AML before chemotherapy and autologous BMT. Disease-free survival was 30% and the relapse rate 68%. Twenty-one patients were transplanted for MDS or AML which had developed after treatment with chemotherapy for other malignancies or autoimmune diseases. Actuarial disease-free survival of these patients was 36% and the relapse rate 60%. Patients younger than 40 years had a significantly (\( P = .004 \)) better disease-free survival as compared with patients with age > 40 years. The difference could be explained by a significantly higher relapse rate (72%) in the older age group as compared with the younger patients (59%) (\( P = .05 \)). Transplant-related mortality and death due to failure to engraft did not appear to occur more often than after autologous BMT for de novo AML. However, hematopoietic engraftment was slower despite a sufficient number of colony forming units-granulocyte macrophage (CFU-GM) collected—a situation similar to that observed in de novo AML patients. Laporte reported the results of autologous BMT with mafosfamide treated marrow in seven patients with AML after MDS. Hematopoietic engraftment was slow in these patients, too, but all of them engrafted except for one patient who died early of treatment-related causes. Two patients were alive and well 10 and 28 months after autologous BMT. Six patients received autologous peripheral blood progenitor cells in a prospective study of the European Organization for Research and Treatment of Cancer (EORTC) leukemia cooperative group and the EBMT. Peripheral blood stem cells were collected during the recovery phase of the first consolidation course, G-CSF was used to mobilize peripheral blood stem cells. Preliminary data indicate that repopulation after transplantation of peripheral blood stem cells was much faster as compared with autologous BMT.

In summary, any patient suffering from MDS or secondary AML who is younger than 55 years should be offered an allogeneic BMT if an HLA-identical sibling or a closely matched family donor is available. The search for a matched unrelated marrow donor has become increasingly successful over recent years and
may be particularly rewarding for children and younger adults. Most patients may benefit most from an early transplant as soon as the diagnosis is confirmed and a suitable donor has been identified. Delay of the transplant carries the risk of progression of the disease. Transplantation of patients with an elevated percentage of blast cells in the marrow, however, is associated with a higher failure rate mainly due to an increased probability of relapse after BMT. Delay of the transplant may be justified in a minority of RA or RARS patients without cytopenia or complex cytogenetic abnormalities, without leukemic in vitro growth characteristics and no need for erythrocyte or platelet transfusions. All patients including those without excess of blasts should be conditioned with bone marrow ablative therapy rather than an immune suppressive regimen, such as cyclophosphamide alone. Total body irradiation has been included in most BMT conditioning regimens, but preparation with a combination of busulfan and cyclophosphamide may produce similar results. The pattern of continued relapse in RAEB and RAEB-t patients beyond 1 year is reminiscent of chronic myelogenous leukemia. Whether more intensive conditioning regimens or intensive polychemotherapy prior to the transplant procedure would yield better results is unknown at present. Younger patients not eligible for an allogeneic BMT are candidates for new experimental strategies like an autologous marrow transplant within the frame of clinical studies. Recent reports demonstrating the presence of polyclonal hematopoietic progenitors in mobilized peripheral blood of patients with MDS will promote the use of PBPC instead of bone marrow cells also in the setting of MDS. Besides the possibility of grafting a patient with normal hematopoietic progenitor cells PBPC should be able to substantially shorten the time to platelet and neutrophil recovery after myeloablative therapy and thus reduce the risk of transplant-related complications.

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