Intensive chemotherapy for poor prognosis myelodysplasia (MDS) and secondary acute myeloid leukemia (sAML) following MDS of more than 6 months duration. A pilot study by the Leukemia Cooperative Group of the European Organisation for Research and Treatment in Cancer (EORTC-LCG)

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We conducted a prospective, multicenter pilot study of remission induction therapy in patients with poor prognosis MDS and AML evolving from a preceding phase of MDS. Fifty evaluable patients from 15 institutions were treated with one or two remission-induction courses consisting of i.v. idarubicin 12 mg/m²/day on days 1, 2, and 3 combined with a continuous i.v. infusion of cytarabine of 200 mg/m²/day on days 1 to 7. Of the 27 complete remitters (54%), 23 received a consolidation course which was identical to the remission-induction course except for the idarubicin 12 mg/m² which was given on day 1 only. Fifteen patients received maintenance therapy consisting of six courses of cytarabine 10 mg/m², s.c. twice daily, for 14 days. Two complete remitters were allografted and five patients received an ABMT. The median survival of all 50 treated patients was 14 months. The median duration of disease-free survival was 11 months with two patients in CR more than 2 years after entering CR. Twenty-four of the 27 remitters have relapsed. Four patients died during remission-induction therapy, but no patient died as a result of persisting hypoplasia. No fatal complications occurred during the consolidation and maintenance courses. Age and stage of disease had no significant impact on CR rate nor on remission duration. The CR rate was significantly (P = 0.03) higher in patients with only normal metaphases compared to patients with cytogenetic abnormalities. The DFS at 2 years was 33 vs 8%, respectively, for patients without or with cytogenetic abnormalities (P = 0.02). This study shows that patients below the age of 60 years with poor risk features are candidates for treatment with combination chemotherapy. A complete remission rate of more than 50% may be expected. Maintaining remission after remission-induction chemotherapy is a difficult issue. Patients not eligible for allogeneic BMT may be treated with intensive post-remission chemotherapy or autologous BMT.

Keywords: myelodysplastic syndrome; secondary acute myeloid leukemia; cytogenetics; chemotherapy

Introduction

Myelodysplastic syndromes (MDS) form a group of disorders of the hematopoietic stem cell with a variety of clinical and laboratory features.1-4 MDS have been classified by the French-American-British (FAB) Group into five subcategories: refractory anemia (RA), refractory anemia with ringsideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEBt), and chronic myelomonocytic leukemia (CMML).5 Clonal cytogenetic abnormalities have been reported in 23-78% of cases with MDS.6,7 In contrast to AML, MDS is often associated with chromosome deletions as a primary karyotypic abnormality. Translocations such as t(8;21) and t(15;17) which are characteristic of certain types of AML are rare.8

The clinical course of the myelodysplastic syndromes varies from an indolent form to a rapidly fatal disease. RA or RARS are characterized by a low risk of transformation to acute myeloid leukemia and a median survival usually exceeding 30 months.9 Median survival of patients with RAEB or RAEBt is less than 12 months despite any treatment given.10 Patients with a normal karyotype have a better prognosis than those with single abnormalities.6,7 Patients with complex cytogenetic abnormalities have the worst prognosis.6,7,11

The generally accepted policy of treatment for most patients with MDS is supportive therapy.12 Androgens,13 low-dose cytarabine,14 vitamin A and vitamin D analogs15,16 have been assessed in pilot studies, but failed to induce a substantial percentage of complete remission or better survival than the control group treated with supportive care only.17-19 Administration of recombinant granulocyte-macrophage colony-stimulating factor, erythropoietin and interleukin-3, alone or in combination, induced clinically relevant responses in some patient categories, but overall survival was not influenced.20-25

More intensive treatment approaches are being explored in younger patients in view of the relatively short median survival of less than 12 months in most categories of patients. Some young patients may achieve prolonged, disease-free survival after treatment with combination chemotherapy.26-28 Prospective, multicenter studies have not been performed in patients with MDS.

For these reasons we initiated a prospective, multicenter pilot study of remission-induction therapy, similar to the treatment of de novo AML in patients younger than 60 years of age, for patients with poor prognosis MDS and AML evolving from a phase of MDS. In view of promising preliminary studies it was decided to replace the conventional anthracycline, daunorubicin, by the potentially more active anthracycline 4-demethoxydaunorubicin (idarubicin).29,30 The major aim of this study was to assess the value and toxicity of remission-induction combination chemotherapy in poor prognosis and transformed MDS in terms of partial and complete response rate, duration of hypoplasia and death rate during hypoplasia. The second aim of the study was to assess the feasibility and toxicity of a less intensive consolidation course followed by maintenance therapy with six courses of low-dose cytarabine in those patients not eligible for allogeneic BMT. The final aim was to study overall survival and disease-free survival (DFS).
Patients and methods

Patient selection criteria

The following patients were eligible for study: (1) patients with refractory anemia (RA), RA with ringsideroblasts (RAS) or RAEB with ≤10% blasts in the marrow and multiple chromosomal abnormalities; (2) RAEB with >10% blasts in the bone marrow; (3) all patients with RAEB in transformation (RAEBt); (4) chronic myelomonocytic leukemia (CMML) with a neutrophil count of >16 × 10^9/l or a monocyte count of >2.6 × 10^9/l in the blood or 5% blasts in the bone marrow; and (5) all patients with secondary AML supervening on overt MDS of more than 3 months duration.

Exclusion criteria were the following: (1) age less than 15 years or more than 60 years; (2) previous intensive chemotherapy, and/or radiotherapy for MDS or AML; (3) treatment with biological response modifiers and/or low-dose cytarabine for the idarubicin which was given on day 1 only in the same center. In case of a HLA-A, -B, -Dr identical, MLC nonreactive, the patient was proposed for allografting. The allo-BMT was planned as soon as possible after recovery from the consolidation course. Patients not eligible for allo-BMT were scheduled to receive maintenance therapy consisting of six courses of cytarabine 10 mg/m², s.c. twice daily, for 14 days with 4-week intervals between the courses.

Design of the protocol

The remission–induction course consisted of idarubicin 12 mg/m²/day as a 5 min i.v. injection on days 1, 2, and 3 combined with a continuous i.v. infusion of cytarabine of 200 mg/m²/day on days 1 to 7 (total 7 days). In case of partial response one additional identical remission–induction course was to be given. The remaining patients with a poorer response were taken off study. Patients entering a CR after one or two courses of remission therapy received consecutively one consolidation course starting 4 weeks after the beginning of the (last) remission–induction course. The consolidation course was identical to the remission–induction course except for the idarubicin which was given on day 1 only in the same dosage of 12 mg/m².

HLA-typing of patients, parents and siblings was initiated at the onset of induction therapy in all patients younger than 40 years (or younger than 50–55 years according to the policy of the center). In case of a HLA-A, -B, -Dr identical, MLC nonreactive sibling, a one locus class-I mismatched sibling or a phenotypically identical parent, the patient was proposed for allografting. The allo-BMT was planned as soon as possible after recovery from the consolidation course. Patients not eligible for allo-BMT were scheduled to receive maintenance therapy consisting of six courses of cytarabine 10 mg/m², s.c. twice daily, for 14 days with 4-week intervals between the courses.

Required clinical investigations

Pretreatment bone marrow and blood smears were centrally assessed by the MDS section of the pathology review committee of the EORTC-LCG (coordinator: Dr H Zwierzina). The classification of MDS and AML was performed according to the criteria of the FAB working group. One smear of bone marrow and blood was also reviewed centrally at the time of CR or first relapse. Apart from the other standard investigations it was strongly recommended to perform cytogenetic analysis with banding techniques prior to the start of chemotherapy.

Definitions

AML evolved from myelodysplasia was defined as secondary AML (sAML). AML after chemotherapy or radiotherapy was defined as therapy-related AML (t-AML).

Complete remission (CR) was defined as absence of clinical manifestations of leukemia and less than 5% blasts in a normocellular marrow with normal morphology. The peripheral blood neutrophil count should be ≥1.5 × 10^9/l and platelets more than 100 × 10^9/l. Normalization of cytogenetic abnormalities was not included in the definition of CR.

Partial remission was defined as 50% or more reduction of blasts in a normocellular marrow.

The duration of survival was calculated from the date of start of treatment until death. For patients who achieved CR after induction the DFS was calculated from the date of first CR until the date of first relapse or the date of death in first CR. The duration of survival of remitters corresponds to the time for first CR to the date of death or date of last follow-up.

Statistical methods

All patients were prospectively registered at the EORTC Data Center in Brussels. The relationship between the disease stage of the patient (MDS vs sAML) or response to induction (CR vs no CR) and different initial features was statistically tested using the x² test. The x² test for linear trend was used. The differences between curves were statistically tested using the two-tailed log-rank test. For ordered variables the log-rank test for linear trend was used.

Results

Clinical data

Fifty-one patients from 15 institutions were registered between September 1989 and March 1993. Sufficient data for evaluation was available for 50 patients. The youngest patient was 17 years old and the oldest patient was 60 years old. The median age was 46 years. Clinical data are presented in Table 1. Thirty-four patients had a form of MDS when chemotherapy was available for 50 evaluable patients with MDS or sAML.

Table 1 Clinical data of 50 evaluable patients with MDS or sAML treated with 3/7 idarubicin/cytarabine

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDS</th>
<th>sAML</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>34</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>FAB subtypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEBt</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMML</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy-related MDS/sAML</td>
<td>3</td>
<td>5</td>
<td>0.11</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49 years</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>50–80 years</td>
<td>12</td>
<td>10</td>
<td>0.014</td>
</tr>
<tr>
<td>Cytogenetic studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not performed/no metaphases</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Only normal metaphases</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Normal/abnormal metaphases</td>
<td>14</td>
<td>5</td>
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<tr>
<td>Only abnormal metaphases</td>
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<td>4</td>
<td>NS</td>
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<td>Simple abnormalities</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multiple abnormalities</td>
<td>18</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant
was initiated. Nine patients had RAEB, four patients CMML, and 21 patients were classified as RAEBt. Sixteen patients had progressed to AML prior to starting chemotherapy.

**Treatment results**

Twenty-six patients (52%) entered CR after one remission-induction course. Six patients received a second remission-induction course. One additional patient entered CR after administration of the second remission-induction course. Nine patients with cytogenetic abnormalities prior to remission-induction therapy were re-evaluated cytogenetically after having entered CR. A median number of 20 metaphases (range 10–73) were analyzed. Eight patients showed normal metaphases while one patient had persistent abnormal metaphases. Two additional patients showed normal metaphases during remission.

Four patients died during the remission-induction courses. Two died from toxic complications and two from infectious complications. None died from persistent or prolonged hypoplasia. Five patients achieved partial remission. Fourteen patients had either progression of the disease despite therapy or the disease status remained unchanged. None of the patients remained hypoplastic after the remission-induction courses.

Intensive salvage chemotherapy was administered to four patients outside the protocol. One of these four patients achieved a CR, but the disease status of the other three patients remained unchanged. One of these patients received an allogeneic BMT from a mismatched sibling and died from treatment-related complications. Two patients died from relapse after allo-BMT and one patient died from veno-occlusive disease.

Twenty-seven patients were scheduled to receive the consolidation course. Four patients did not receive the consolidation course in first CR due to poor clinical performance (two patients) or early relapse (two patients). All 23 patients who received the consolidation course maintained CR. Twenty-three patients were eligible for treatment with six courses of low-dose Ara-C. Two had a compatible donor and were scheduled for allo-BMT. An autologous bone marrow transplantation (ABMT) was planned for a further six patients (performed in five patients). The remaining 15 patients received either all six courses (12 patients), five courses (one patient), or four courses (two patients). Three of these 15 patients are alive and well in second CR 41 months after the second BMT. The other three patients with a donor did not achieve CR and were transplanted in partial remission. Two patients relapsed and the third died from treatment-related causes.

Five patients received an ABMT. Only the patient who had been transplanted after a CR duration of 666 days remained in CR. The other four patients have relapsed.

**Overall results**

The median duration of survival of all 50 treated patients was 15 months (Figure 1a). Twelve patients were alive 2 years after registration. The median duration of survival of the 27 com-

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**Bone marrow transplantation**

Family typing was performed in 16 of 31 patients younger than 50 years. Only ten patients were younger than 40 years. The policy to perform allogeneic BMT in patients between the age of 40 and 50 years varied from center to center. Five patients had an identical sibling. Two of these patients achieved CR. One patient was transplanted in first CR. He relapsed 5 months after BMT, but was retransplanted without a further attempt to induce remission prior to the BMT. He is alive and well in second CR 41 months after the second BMT. The other patient was transplanted in first relapse but died from relapse after BMT. The other three patients with a donor did not achieve CR and were transplanted in partial remission. Two patients relapsed and the third died from treatment-related causes.

Five patients received an ABMT. Only the patient who had been transplanted after a CR duration of 666 days remained in CR. The other four patients have relapsed.

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**Figure 1** (a) Actuarial survival of all 50 evaluable patients. N: number of patients; O: number of observed events. (b) Actuarial survival (solid line) or disease-free survival (dashed line) of 27 patients who reached CR after one or two remission-induction courses.
plete remitters was 21 months. The median disease-free survival was 11 months with two patients in CR more than 2 years after entering CR (Figure 1b). Twenty-two of the 27 remitters have relapsed and two patients have died in CR.

**Toxicity of chemotherapy**

The toxicity was graded according to the standard WHO criteria. The major observed toxicity was infection during remission induction and the consolidation course (Table 2). Four patients died during remission–induction therapy. Two patients died during the first week of therapy due to multi-organ failure and cardiac toxicity, respectively. One patient died on day 28 after initiation of therapy, mainly due to infectious complications, and the fourth patient died after the second remission–induction course was administered. The toxicity was significantly more frequent in patients who were treated after progression to AML. The median DFS was 7 months for the patients with MDS and 17 months for the patients with AML.

**Hospitalization duration**

The median number of days spent in hospital during and following the first remission–induction course was 30 days with a range between 24 and 80 days. The three patients who died during this course were excluded. The median duration of hospitalization of the 26 patients who entered CR after one remission–induction course was 31 days with a range of 24–44 days. The median time interval between start of remission–induction therapy and start of consolidation therapy was 40 days. All 23 patients who entered CR after one course of remission–induction therapy and who received consolidation therapy started the consolidation course within 8 weeks after start of remission–induction therapy.

**Prognostic variables**

Several variables have been analyzed in order to assess their prognostic value. Leukocyte count, platelet count, marrow cellularity, the presence of Auer rods (present in five patients only) and the duration from diagnosis of MDS to start of chemotherapy had no major impact on treatment outcome (data not shown).

**MDS vs sAML**

Thirty-four patients with MDS were treated with one or two remission–induction courses and 17 patients (50%) achieved CR. Five out of nine patients (55%) with the morphological picture of RAEB, 10 of the 21 patients (48%) with RAEBt and two of the four patients with CMML (50%) entered CR. Ten of 16 patients (63%) with AML at initiation of chemotherapy achieved CR. The CR rates between the different subgroups were not significantly different. The median survival of the 34 patients with MDS was 12 months compared to 21 months for the 16 patients with sAML ($P = 0.18$). The DFS was significantly longer ($P = 0.03$) for those patients who were treated after progression to AML. The median DFS was 7 months for the patients with MDS and 17 months for the patients with AML.

**Age**

Significantly ($P = 0.014$) more younger patients had the morphological picture of MDS at the start of treatment (Table 1). Sixteen of the 31 patients (52%) younger than 50 years entered CR and 11 of the 19 patients (58%) older than 50 years. Survival and DFS were similar in both age groups (data not shown).

**Therapy-related MDS/sAML**

Eight patients had been treated with cytotoxic agents for other malignancies or auto-immune disorders. Five of these patients had progressed to AML. Two of the eight patients with therapy-related MDS/AML entered CR (25%) and 25 of the 42 primary cases (60%). These differences did not reach significance ($P = 0.15$), mainly due to the low numbers. The overall survival at 3 years of the 42 primary patients was 29 vs 12% for eight patients with therapy-related MDS/AML ($P = 0.28$).

**Cytogenetics**

No cytogenetic data were available on five patients. In 10 patients only normal metaphases were found. Thirty-five patients had cytogenetic abnormalities (Table 1). Only one of these patients had a chromosomal abnormality associated with de novo AML. In this patient with a RAEBt a t(8;21) was observed in all 25 metaphases. This patient entered CR, but relapsed after 17 months. Cross tabulation of the cytogenetic data with other pretreatment variables did not disclose any significant association. However, six of the eight patients with post-cytotoxic MDS/AML showed cytogenetic abnormalities ($P = 0.3$). The CR rates of groups stratified according to presence or absence of chromosomal abnormalities is shown in Table 3. The CR rate was significantly ($P = 0.03$) higher in patients with only normal metaphases compared to patients with cyto-

<table>
<thead>
<tr>
<th>Table 2 Toxicity of chemotherapy*</th>
<th>Remission–induction course</th>
<th>Consolidation course</th>
<th>Maintenance courses</th>
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<tbody>
<tr>
<td>Number of evaluable patients</td>
<td>50</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Infection</td>
<td>36</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardio-vascular</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Only toxicities of >grade 1 according to WHO criteria.
genetic abnormalities. The 2-year survival was 50% of the 10 patients with no cytogenetic abnormalities, while 21% of the patients with abnormal metaphases survived 2 years after registration (Figure 2a). This difference was statistically different ($P = 0.02$). The DFS at 2 years was 8 vs 33%, respectively, for patients with or without cytogenetic abnormalities ($P = 0.02$) (Figure 2b). Two of the three patients still in CR at the time of analysis had no chromosomal abnormalities, but the marrow of the third patient showed multiple chromosomal abnormalities before start of treatment.

**Table 3** Influence of cytogenetic abnormalities on CR rate

<table>
<thead>
<tr>
<th>Cytogenetic data</th>
<th>Number of patients</th>
<th>CR (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No data</td>
<td>5</td>
<td>2 (40)</td>
<td></td>
</tr>
<tr>
<td>Only normal (NN)</td>
<td>10</td>
<td>9 (90)</td>
<td></td>
</tr>
<tr>
<td>Other (AN + AA)</td>
<td>35</td>
<td>16 (46)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Figure 2** (a) Actuarial survival of 10 patients with normal cytogenetic metaphases (NN) prior to treatment (solid line) and 35 patients with abnormal metaphases (AN-AA) prior to treatment (dashed line). N: number of patients; O: number of observed events. NN: only normal metaphases; AN: normal and abnormal metaphases; AA: only abnormal metaphases. (b) Actuarial disease-free survival of nine patients with normal cytogenetic metaphases (NN) prior to treatment (solid line) and 16 patients with abnormal metaphases (AN-AA) prior to treatment (dashed line).

Conventional, multidrug chemotherapy, used to induce complete remission (CR) in *de novo* AML, has been demonstrated to be effective in MDS with CR rates varying from 15 to 64%. In the present, prospective, multicenter study 27 out of 50 evaluable patients (54%) achieved CR. One additional patient entered CR after salvage chemotherapy resulting in an overall CR rate of 56%. The remission status was confirmed by cytogenetic analysis in the majority of patients with cytogenetic abnormalities prior to treatment. Cytogenetic analysis in remission was performed in nine of the 16 remitters with cytogenetic abnormalities prior to treatment. Eight of nine patients showed only normal metaphases.

The high failure rate of remission-induction therapy can be explained partly by the long duration of hypoplasia after chemotherapy, but also by a high drug resistance of the leukemic clone. A long duration of hypoplasia after remission-induction therapy has been reported by several groups. This resulted in a toxic death rate ranging from 14 to 21%. The prolonged period of hypoplasia has not been shown to be consistent in all studies. In the current study, the toxic death rate during induction therapy was only 8%. The duration of hypoplasia was not recorded, but the average duration of hospitalization during and after the first remission-induction course lasted only 30 days which suggests a relatively fast marrow recovery. Moreover, no fatalities occurred during prolonged hypoplasia.

Untreated cases of myelodysplastic syndromes appeared to have a higher incidence of the multidrug phenotype associated with the P-glycoprotein (PGP) compared to *de novo* AML. CR was achieved more frequently in PGP-negative cases after treatment with intensive anthracycline-Ara-C chemotherapy compared to PGP-positive cases. In the current study, relative (five patients) or absolute resistance (14 patients) was the major reason of failure of this relatively mild remission-induction therapy.

Some patients with MDS in CR after combination chemotherapy may achieve prolonged, disease-free survival, but overall median remission duration was short and usually less than 12 months. In the present study, only three out of the 28 remitters have remained in first CR, but four additional patients entered a second CR of substantial duration. The median survival duration of the complete remitters was 21 months and 38% of these patients were still alive 2 years after registration. The overall survival at 2 years was 27% (Figure 1).

Several prognostic characteristics may be identified in MDS and sAML. Patients with the morphological picture of RAEB and RAEBt seemed to respond favourably to intensive chemotherapy, approaching remission rates of those seen in *de novo* AML. Patients with secondary AML evolved from MDS responded less well to chemotherapy than did those with *de novo* leukemias and long-term remissions were rare. Certain subcategories of patients with sAML may show response rates similar to *de novo* AML. Patients with the morphologic picture of RAEB or RAEBt responded less well in this study compared to the patients who had progressed to AML. The DFS or sAML patients was significantly ($P = 0.03$) better in the current study despite a younger age in the MDS patient group and a shorter interval between diagnosis and treatment. The explanation for this may be the relatively high number of MDS patients with cytogenetic abnormalities: 26 out of 34 patients. The clinical outcome after intensive chemotherapy for therapy-related MDS and AML (t-
MDS/AML) is generally poor with only a low number of patients surviving beyond 1 year.26,41 In the present study, none of the eight therapy-related MDS or AML survived for more than 3 years after initiation of chemotherapy.

Some groups have reported data on patients initially diagnosed as having de novo AML and retrospectively reclassified as MDS.34,42 These patients probably represent a subcategory of MDS with a short history plus clinical and/or cytogenetic features resembling de novo AML. Results of combination chemotherapy in this category of patients may be better than in the general population of patients with MDS. Bernstein43 observed no relevant differences of response rates and survival in patients retrospectively reclassified as RAEB, RAEBt or AML treated with front line CALGB AML protocols. Similarly MDS patients treated within 3 months of diagnosis showed a better response to intensive chemotherapy.44 In this study all patients were to have clear-cut MDS or AML after a well-defined preceding phase of MDS of at least 3 months duration. The cytogenetic data here support the myelodysplastic nature of the patients in this study. Only one patient had chromosomal abnormalities associated with de novo AML. Moreover, 35 out of the 50 patients had clonal chromosomal abnormalities. The presence of cytogenetic abnormalities specific for MDS, such as abnormalities of chromosomes 5 or 7 has a major negative impact on the prognosis after combination chemotherapy. Fenaux et al.45 observed a CR rate of 57% in MDS patients with a normal karyotype contrasting with a CR rate of 31% in patients with rearrangements of chromosomes 5 or 7. In this study patients with only normal metaphases in the bone marrow had a significantly better outcome compared to patients with chromosomal abnormalities. The numbers were too small to allow analysis of certain subgroups of patients.

ABMT has been performed in an occasional patient with MDS or sAML.44,45 ABMT was not recommended within the present study. Nevertheless, five patients were treated with ABMT. Four patients have relapsed and only one patient remains in CCR. No conclusions can be drawn from this limited number of patients.

Allogeneic BMT is considered to be the treatment of choice for young patients (age below 55 years) with MDS or sAML if an HLA-identical sibling donor is available.46-49 If allogeneic BMT for MDS is performed during a stage of excess of blasts (RAEB or RAEBt) or during overt transformation then a relapse risk of 50-80% may be expected.48,49 For that reason most European centres elected to treat these patients with allo-BMT after an attempt to induce CR with chemotherapy.50 In this study, five patients were allografted with marrow from an identical sibling. Four patients were transplanted after failure of remission-induction therapy. Two patients relapsed after BMT and two patients died due to transplant-related complications. One patient received the allograft in first CR, relapsed 5 months after BMT, but achieved second CR 41 months after second BMT with signs of mild chronic graft-versus-host disease. The first graft consist of bone marrow depleted of T lymphocytes by counterflow elutriation51 whilst the second graft was carried out using unmanipulated marrow.

The data of this study show that patients below the age of 60 years with poor risk features may be considered for treatment with combination chemotherapy. A complete remission rate of more than 50% may be expected. Failure to achieve CR was not due to persisting marrow aplasia or due to a high treatment-related fatality but due to persisting disease. Maintaining remission after remission-induction chemotherapy is difficult. Patients not eligible for allogeneic BMT could be treated with intensive, post-remission chemotherapy or autologous BMT preferentially within the frame-work of prospective studies. The ongoing EORTC/EBMT study for this patient category evaluates the role of a more intensified remission-induction schedule followed by an intensive consolidation and either autologous stem cell transplantation or allogeneic bone marrow transplantation.

Acknowledgements

The authors acknowledge gratefully Dr BM Dale, Queen Elizabeth Hospital, Woodville, South Australia for his comments and advice. This publication was supported by grant numbers 5U10-CA11488-19 to 2U10-CA11488-25 from the National Cancer Institute. The contents are solely the responsibility of the authors and do not represent the official views of the National Cancer Institute.

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