Anti-Leukemia Chemotherapy of High-Risk Myelodysplastic Syndromes

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ABSTRACT

We evaluated the outcome of anti-leukemia chemotherapy on 42 patients with the high-risk myelodysplastic syndromes (MDS)—refractory anemia with excess of blasts (RAEB), 8 cases; RAEB in transformation (RAEB-T), 18 cases; chronic myelomonocytic leukemia (CMMOL), 6 cases; and leukemic transformation of MDS, 10 cases. The median age was 67 (range 20 to 84). As a remission-induction therapy, 35 patients received low-dose chemotherapy, such as low-dose cytarabine infusion, and seven patients received high-dose combination chemotherapy. The complete remission (CR) rates of the low-dose chemotherapy group and the high-dose combination chemotherapy group were 29% and 57%, respectively, and the overall CR rate was 33%. The median survival durations after induction chemotherapy of the CR group (14 cases), the partial remission (PR) group (11 cases), and the non-remission (NR) group (17 cases) were 19 months, 8 months, and 3 months, respectively. As a post-remission consolidation chemotherapy, high-dose combination chemotherapy seemed to be superior to low-dose chemotherapy judging from the median CR duration (16 months versus 4 months), but a long-term disease-free survival is hardly expected, in contrast with results in cases of de novo acute myeloid leukemia.

INTRODUCTION

Although great progress has been achieved on the treatment of hematological disorders, the myelodysplastic syndromes (MDS) are still intractable clonal hemopathy [1-3]. Among the five subtypes of the French-American-British classifications, refractory anemia with excess of blasts (RAEB), RAEB in transformation (RAEB-T) and chronic myelomonocytic leukemia (CMMOL), the so-called high-risk MDS, are always exposed to the danger of fatal leukemic transformation (LT-MDS) [4, 5]. Median survival of patients with RAEB or RAEB-T is less than 12 months despite any treatment given [6]. To improve the poor prognosis of the high-risk MDS, more intensive treatments, including bone marrow transplantation, are being explored, mainly in younger patients [7]. In this report, we evaluate retrospectively the preliminary results of remission-induction chemotherapy on high-risk MDS in a single institution and search for a better maintenance therapy for these malignant disorders.

PATIENTS AND METHODS

Patients

Among 76 adult patients with MDS (52 patients were diagnosed with high-risk MDS and 24 with low-risk MDS) who were admitted to Fukui Medical School from 1983 to 1994, 42 patients received anti-cancer chemotherapy and were eligible for this study. All of the 42 patients were diagnosed with high-risk MDS, including cases of LT-MDS. The ages ranged from 20 to 84 years (median age 67), and the male/female ratio was 30/12. The classification of the patients is shown in Table 1.

Chemotherapy Protocols

Table 1 also divides the patients into two groups which received low-dose chemotherapy and high-dose combination chemotherapy, respectively, as remission-induction treatments. The low-dose and high-dose chemotherapy regimens,
including low-dose cytarabine [8] and high-dose BHAC combinations, are detailed in Table 2. The patients who had achieved complete remission (CR) subsequently received some maintenance chemotherapy.

Evaluation of Chemotherapeutic Effects
Chemotherapeutic effects were evaluated in accordance with those of acute leukemia. That is, the patients whose bone marrow showed both the decrease in the blast percentage to below 5% and the recovery of trilineage hematopoiesis were judged to be in CR, and the cases whose bone marrow showed both the decrease in the blast percentage to some degree and the improvement of cytopenia were judged to be in partial remission (PR).

Statistical Analysis
The survival curves were compared statistically using the Wilcoxon’s test.

RESULTS AND DISCUSSION
Of 42 patients with the high-risk MDS, 35 patients received low-dose chemotherapy and seven patients the high-dose combination chemotherapy for remission-induction (Table 1). Table 3 shows the results of induction therapy. Overall CR rate was 33% and obviously inferior to that of de novo acute myeloid leukemias (AML) in our hospital (the CR rate is approximately 70%). Among the subtypes of high-risk MDS, RAEB-T revealed the most preferable response (CR: 50%; CR + PR: 72%). There is no denying the possibility that some of AML-M2 cases at the early stage were slipped into the RAEB-T group, but the poor long-term survival rate as described below does not correspond with such a possibility. RAEB-T cases might be able to achieve remission easily as compared with RAEB cases, although the remission does not lead to the long-term survival, in contrast with results of de novo AML cases.

Table 4 shows the further results of remission induction classified by treatments—low-dose chemotherapy or high-dose combination chemotherapy. The CR rates of the low-dose chemotherapy group and the high-dose combination chemotherapy group were 29% (10/35) and 57% (4/7), respectively. In 10 complete remitters of the low-dose chemotherapy group, five cases achieved CR by one course of chemotherapy, but the remaining five cases needed two courses for CR. Likewise, in four complete remitters of the high-dose combination chemotherapy group, two cases achieved CR with one course of chemotherapy, but the remaining two cases needed two courses for CR. Indeed, it is difficult to evaluate the...
difference of the CR rates because the patient number was small and their profiles, such as the age range, were not matched, but probably the high-dose combination chemotherapy can be expected to result in a more favorable outcome [5, 9-15]. Next, we compared the survival durations after the induction chemotherapy between the CR group (14 cases), the PR group (11 cases), and the non-remission (NR) group (17 cases). The CR group achieved a median survival of 19 months (range 4 to over 40 months). In contrast, the PR group and the NR group represented median survival durations of eight months (range 3 to 22 months) and three months (range 1 to 34 months), respectively. Figure 1 shows these results as the survival curves after chemotherapy. It should be noticed that even the CR group does not draw a plateau curve, but a descendent pattern, which means no curative probability, although a statistical analysis represented a significant difference between the CR group and the other groups. Seven patients among 14 CR cases died of LT-MDS and four patients succumbed to non-leukemic death. The survival curve of the CR group is clearly different from that of de novo AML cases which initially form a descending but subsequently plateau curve, as experienced in most institutions. Non-CR groups, including the PR group, followed quite miserable courses (50% survival: six months). Clinical hematologists who have successfully induced high-risk MDS patients to CR are often embarrassed about the selection of subsequent consolidation or maintenance chemotherapy. In this study, 10 patients entered CR by low-dose chemotherapy (as shown in Table 4), and the median CR duration was eight months. Of these 10 patients, five patients received repeatedly low-dose chemotherapy and the remaining five patients received high-dose combination chemotherapy completely different from the remission-induction therapy. The median CR durations of the former and the latter were four months and 16 months, respectively. In spite of a small case study, these data suggested that high-dose intensive chemotherapy as the consolidation possibly leads to a longer CR duration.

Various therapeutic approaches have been used to improve the clinical disorders caused by MDS [15, 16-19]. The concept of the therapy of MDS can be divided as follows: A) the improvement of cytopenia by blood transfusion, steroids, and cytokines; B) the differentiation-induction of the abnormal clones by certain chemical agents or cytokines; C) the extermination of pre-leukemic blast cells by chemotherapy with anti-cancer drugs; D) the replacement of hematopoietic stem cells by stem cell transplantation, and E) the immune therapy by immunomodulating agents. However, no curative treatment has yet been established other than allogeneic bone marrow transplantation [20-22]. Our study corresponds to therapy C, the extermination of pre-leukemic blast cells by chemotherapy with anti-cancer drugs, but may not offer a confidence that such anti-cancer chemotherapies actually contribute to a long-term disease-free survival of the high-risk MDS patients. The results of cytogenetic analysis were eliminated from this study.

### Table 3. Results of remission-induction therapy

<table>
<thead>
<tr>
<th>Clinical subtypes</th>
<th>n of cases</th>
<th>CR cases</th>
<th>PR cases</th>
<th>CR &amp; PR cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAEB</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>18</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>CMMOL</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>LT-MDS</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total (%)</td>
<td>42</td>
<td>14</td>
<td>11</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 4. Results of remission-induction therapy classified by treatments

<table>
<thead>
<tr>
<th>Clinical subtypes</th>
<th>n of cases</th>
<th>Chemotherapy</th>
<th>CR cases</th>
<th>PR cases</th>
<th>CR &amp; PR cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAEB</td>
<td>8</td>
<td>Low-dose</td>
<td>8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>18</td>
<td>Low-dose</td>
<td>16</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CMMOL</td>
<td>6</td>
<td>Low-dose</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LT-MDS</td>
<td>10</td>
<td>Low-dose</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total (%)</td>
<td>42</td>
<td>Low-dose</td>
<td>35</td>
<td>10</td>
<td>20 (58%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose</td>
<td>7</td>
<td>4 (57%)</td>
<td>1 (14%)</td>
</tr>
</tbody>
</table>

Wilcoxon: CR versus PR 0.0119
Wilcoxon: CR versus PR+NR 0.0006

**Figure 1. Survival curves of the patients with high-risk MDS after remission-induction chemotherapy.** Patients were divided into CR, PR, or NR groups, and the survival curves were compared statistically using the Wilcoxon’s test.
because the karyotype of the bone marrow was not examined systematically, but it would be a serious biological marker in deciding the prognosis of the MDS patients. Recently, several lines of clinical trials have been conducted [7, 15, 23-25], but further accumulation of prospective multicenter pilot studies as to maintenance therapy of the high-risk MDS is needed to overcome the poor prognosis of these malignant disorders.

REFERENCES