Treatment of blastic phase chronic myeloid leukemia with mitoxantrone, cytosine arabinoside and high dose methylprednisolone

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Abstract—Fourteen patients with blastic phase chronic myelogenous leukemia received combination chemotherapy with mitoxantrone 5 mg/m² intravenously daily for 3 days, cytosine arabinoside 100 mg/m² intravenously over 2 hours bid for 7 days and high dose methylprednisolone 1000 mg/day intravenously for 5 days. The patients’ mean age was 52 ± 10 (range 34–64) and Philadelphia chromosome was positive in all. Five patients (35%) achieved complete remission and four patients (28%) had a partial remission. Overall remission rate was 64%. The mean survival was 11.1 ± 8.6 months (median 13) for all patients, 19.4 ± 4.0 months (median 19) for those achieving a complete remission, 12.50 ± 5.7 months (median 14) for patients with partial remission and 1.8 ± 1.8 months (median 2) for the unresponsive patients. Two of 5 unresponsive patients died early after the second course of remission induction. The treatment regimen was generally well tolerated. Marrow hypoplasia was observed in 9 (64%) patients and 7 (50%) had febrile episodes. Non-myelosuppressive toxicity of the regimen was acceptable. Nausea and vomiting were observed in 8 (57%) patients and 3 (21%) patients developed flushing due to cytosine arabinoside. These results suggest that the regimen with mitoxantrone, cytosine arabinoside and high dose methylprednisolone in remission-induction of blastic phase chronic myelogenous leukemia may be a valid option that may also improve overall prognosis.

Key words: Chronic myelogenous leukemia; blastic phase; high dose methylprednisolone.
INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative haematopoietic stem cell disease characterized by granulocytosis, granulocytic immaturity, basophilia and frequently thrombocytosis [1]. One to five years after onset, the majority of patients evolve into accelerated phase or blastic crisis [2]. Diagnosis of blastic phase requires the presence of 30% blasts either in peripheral blood or bone marrow, or extramedullary blastic disease [3]. Two-thirds of cases have similar phenotype with acute myeloblastic leukemia (AML). In the remaining one-third cases, the blasts have a lymphoid morphology and express lymphoid markers, such as terminal deoxynucleotidyl transferase or CD 10 (common antigen). The blastic crisis of CML is the most malignant form of all acute leukemias. The complete remission (CR) rate is less than 30%, even with intensive chemotherapy, and the median survival is 3–6 months [4, 5].

Cytosine arabinoside (Ara-C) is an effective agent in acute leukemia, and also favorable results have been reported in CML blastic crisis. Mitoxantrone is an anthracenequinone derivative. The combination of these two drugs in different regimens have been reported to achieve response rates of 20–80% in acute leukemia and 20–40% in CML blastic crisis [5–8]. The lack of overlapping toxicities and possible synergistic anti-tumor effects led to use of this combination in several trials in AML with encouraging results [9, 10]. High dose methylprednisolone (HDMP) treatment induces differentiation and apoptosis of leukemic cells of patients with AML in vivo [11, 12]. Also, HDMP improves long-term event-free survival in acute lymphoblastic leukemia and in CML blastic crisis [13, 14]. In this report, we summarize our experience with the combination of mitoxantrone and Ara-C with HDMP in the CML blastic crisis.

MATERIALS AND METHODS

In this study we enrolled 14 CML patients with blastic crisis. The ratio of the blastic cells was higher than 30% in peripheral blood smears and bone marrow in all the cases. Patients with lymphoid blastic crisis were resistant to vincristine and prednisolone treatment [15]. Complete history, physical examination, white blood cell counts, chest x-rays were documented before treatment. To confirm morphologic diagnosis, bone marrow cytological and enzymatic staining were performed. Flow cytometric analyses of lymphoid and myeloid markers were obtained in 6 patients with difficulties in the morphologic studies for further differentiation [16]. In the cytogenetic screening 25 metaphase cells were studied by trypsin Giemsa staining techniques [17].

Induction chemotherapy comprised mitoxantrone 5 mg/m² intravenous (i.v.) over 1 hour daily for 3 days, Ara-C 100 mg/m² bid for 7 days and HDMP 1000 mg/day i.v. for 5 days. Patients who had not achieve CR with marrow studies on the 14th day of the first course received a second course of therapy with the same
regimen. Remission criteria were similar with that of acute leukemia [18, 19]. Complete remission was defined as the presence of 5% or fewer blasts in a normocellular or hypocellular bone marrow, in addition to normal peripheral blood counts with no immature myeloid elements (blasts, promyelocytes and myelocytes) and hemoglobin level > 10 g/dl, a leukocyte count of 2–10 × 10³/µl and a platelet count > 100 × 10³/µl. Partial remission (PR) was defined as the presence of 6–25% marrow blasts. With respect to the cytogenetic response patients in complete hematologic remission were further categorized as follows: (1) complete cytogenetic response, if Ph-positive metaphases were reduced to 0%; (2) partial cytogenetic response, if Ph-positive metaphases were reduced to 1–34%; (3) minor cytogenetic response, if Ph-positive metaphases were reduced to 35–95%. The maintenance regimen for patients achieving remission were mitoxantrone and ara-C (three patients) or interferons (two patients).

Statistical analyses

Survival was calculated from the date of start of therapy. Duration of remission was measured from the time of achievement of remission until documented relapse. Differences among groups were compared using chi-squared test for the CR achievement. Survival and remission duration curves were plotted by the Kaplan and Meier method, and differences among the curves were analyzed by the modified Wilcoxon test.

RESULTS

Population study

The mean age of the patients was 52 ± 10 years (range 34–64) and 10 of the 14 were men. All patients had evolved into blastic crisis after a documented chronic phase of CML lasting for a mean of 23.7 ± 12.5 months (median 22, range 7–49). The primary chronic phase CML had been treated with interferon (3–10 million U/day) and hydroxyurea (1–3 g/day). Blast cell morphological type was myeloid in 10 patients, undifferentiated in 3 patients and lymphoid in one patient. All patients had a documented Ph chromosome in their metaphases. Two patients had additional karyotype abnormalities with monosomy 7 and trisomy 8.

Response

Five of the 14 patients receiving mitoxantrone, conventional dose ara-C and HDMP achieved CR and 4 had a PR. Three partial and two minor cytogenetic responses were achieved among patients with CR. Two of 5 unresponsive patients died early after the second course of remission induction. These early deaths were due to progress of leukemia and intra-cranial hemorrhage.
Table 1.
Toxicity of high dose methylprednisolone, mitoxantrone and intermediate dose cytosine arabinoside in chronic myelogenous leukemia in blastic phase (14 patients)

<table>
<thead>
<tr>
<th></th>
<th>Toxicity Mild-moderate</th>
<th>Severe</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow hypoplasia</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Nausea-vomitus</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Skin rash</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia duration (days)</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Platelet requirement</td>
<td></td>
<td></td>
<td>12</td>
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<tr>
<td>Transfusion requirement</td>
<td></td>
<td></td>
<td>11</td>
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<tr>
<td>Hospital stay (days)</td>
<td></td>
<td></td>
<td>19</td>
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</tbody>
</table>

**Remission duration and survival**
Among the five patients who achieved CR, the mean remission duration was 7.2 ± 1.3 months (median 7, range 6–9), and the mean survival was 19 ± 4.0 months (median 19, range 16–24). The mean survival for patients achieving PR was 12.5 ± 5.7 months (median 14, range 5–17). So the mean survival was 16.3 ± 5.8 (median 17, range 5–24) in the responsive patients while it was 1.8 ± 1.8 months (median 2, range 0–4) for the unresponsive ones.

**Toxicity**
The side effects of mitoxantrone, Ara-C and HDMP in CML blastic phase are shown in Table 1. The treatment was well tolerated and the toxicity was acceptable. No grade III–IV emesis was observed. Severe leukopenia was observed in 9 patients. This was associated with infections or fever of undetermined origin requiring hospitalization and IV antibiotic therapy in 7 patients. Eleven febrile episodes (axillary fever > 38°C) occurred in these patients. These included minor infections (4 patients), pneumonia (2 patients), Staphylococcus bacteremia (2 patients) and fever of undetermined etiology (3 patients). Skin rash developed in 5 patients. Conjunctivitis, mucositis and diarrhea were rare (7%, 7%, 14%, respectively). There were no pulmonary or neurotoxicities.

**DISCUSSION**
Blastic phase CML is the most resistant of acute leukemias. Increasing maturation arrest and proliferation are the two major processes leading to progression from chronic phase to blastic crisis [1, 2]. The therapeutic armamentarium in blastic
The treatment of CML blastic phase

Phase of CML is very limited. Since the insufficient response to monotherapy, reported ORs in decitabin, carboplatin, Ara-C, arabinozyl-5-azacytidine and cladribine studies were 26%, 22%, 41%, 44% and 47%, respectively [19–23]. Due to both the heterogeneity and inappropriate selection of patients in previous reports, there are restricted data about the mitoxantrone and conventional dose Ara-C regimen as well as the HDMP monotherapy [14, 15, 19]. The treatment of patients with blastic phase CML with high dose Ara-C remains controversial [5, 19, 21]. Induction of the differentiation of the immature blast cells into more mature elements is another potential therapeutic strategy that has been proposed for acute leukemias. It has been shown that high dose corticosteroids during remission-induction chemotherapy induces differentiation and apoptosis of leukemic cells in patients with various morphological subtypes of acute myeloblastic leukemia and improves long term event-free survival, particularly for high-risk patients with acute lymphoblastic leukemia [11–13]. High dose interferon alpha and hydroxyurea therapy may transform blastic phase CML to chronic phase [24]. Thirty to seventy percent remissions were reported with etoposide, conventional dose Ara-C and carboplatin (VAC); mitoxantrone and high or conventional dose Ara-C; and fludarabine, Ara-C and G-CSF (FLAG) treatment regimens [25–28]. Therapeutic agent STI571 (signal transduction inhibitor number 571) is a rationally developed, potent, and selective inhibitor.

**Figure 1.** Overall survival of the 14 patients with blastic phase of CML treated with high dose methylprednisolone, mitoxantrone and cytosine arabinoside regimen.
for abl tyrosine kinases, including bcr-abl, as well as c-kit and the platelet-derived growth factor receptor tyrosine kinases [29]. In preclinical and clinical studies, it has been shown to selectively kill bcr-abl expressing cells, both \textit{in vitro} and \textit{in vivo}. Integration of STI571 into CML treatment algorithms will require long-term follow-up data from the ongoing phase II and III clinical studies [30, 31].

In this study, 5 (35\%) patients achieved CR, 4 (28\%) had PR and so a total of 9 (63\%) patients achieved remission in the treatment of CML blastic phase with mitoxantrone, conventional dose Ara-C and short term HDMP. The mean survival was $16.3 \pm 5.8$ (range 5–24, median 17) months in responsive patients. The results of this study are encouraging, though an objective comparison with the previous studies is not possible because of the small number and the heterogeneity of the study population and the absence of a control group.

In conclusion, mitoxantrone, conventional dose Ara-C and HDMP combination treatment may be a promising regimen in blastic phase CML. Also, the addition of HDMP as a differentiating and/or cytolytic agent to conventional protocols might increase the remission rate and prolong the duration of remission. Extended randomized prospective clinical studies are needed for further evaluation of this regimen in this group of patients.
Figure 3. Disease-free survival of the five patients in complete remission treated with high dose methylprednisolone, mitoxantrone and cytosine arabinoside regimen.

REFERENCES


