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 haemapoietic 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 lymphoblastic 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