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Treatment of blastic transformation of chronic myelogenous leukemia with mitoxantrone*

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Summary. Twenty-four patients with blastic-phase chronic myelogenous leukemia (CML) were treated with mitoxantrone. The patients included 19 whose cells were Philadelphia chromosome (Ph^1+) and 5 who were either Ph^1- or in whom cytogenetics were not available. Six of the 19 whose cells were Ph^1+ responded and one of those who were Ph^1- responded. The patients were further characterized into lymphoid or nonlymphoid on the basis of terminal deoxynucleotidyl transferase or morphology. Two of the patients with lymphoid transformation and 3 of those with nonlymphoid transformation responded. In 3 patients post-treatment cytogenetic evaluation revealed the presence of Ph^1- metaphases. We conclude that mitoxantrone has modest activity in blCML and that the cytogenetic responses suggest the possibility of greater efficacy in chronic-phase CML.

Introduction

The failure of chemotherapy to eradicate the malignant clone in Philadelphia chromosome positive (Ph^1+), chronic myelogenous leukemia (CML) has led to trials of supralethal therapy, followed by bone marrow transplantation [1] and of biological response modifiers [2] in the treatment of this disease. Although conventional chemotherapy has not been effective, this does not rule out the possibility that some of the new agents currently under investigation may be beneficial for patients in the chronic phase or blastic phase of CML (blCML). In preliminary reports mitoxantrone (Novantrone) showed significant efficacy in acute myeloid leukemia and sufficient activity in blCML to warrant further evaluation [3–5]. In this report we describe our experience with mitoxantrone in a large series of patients with blCML.

Material and methods

Patient entry. Between July 1982 and November 1984, 122 patients were entered onto a multicenter trial evaluating mitoxantrone for refractory acute leukemia, acute leukemia in relapse, and blCML. Of these, 24 patients had a diagnosis of blCML. (Included in this series are the patients reported previously [3, 4]. This required the presence in the bone marrow of greater than 30% blasts plus promyelocytes [6]. The type of blastic transformation was defined further (lymphoid versus nonlymphoid) by routine morphology, histochemistry and, in some cases, measurement of terminal deoxynucleotidyl transferase (Tdt). Cytogenetic evaluation of the bone marrow was done in most cases prior to the start of therapy and then, in selected cases, additional evaluation was made at the time of maximum response. Patients whose bone marrow was Ph^1+ as well as those who were Ph^1- were eligible for treatment.

Treatment and response evaluation. The patients received mitoxantrone 10 to 12 mg/m^2 intravenously daily for 5 days. A bone-marrow aspiration was done at 7–10 days post completion of treatment and, if still leukemic, a second course of mitoxantrone could be administered. A partial response required reduction of the bone marrow blasts plus promyelocytes to less than 30%. A partial true remission required the appearance of Ph^1- metaphases. In a complete true remission, all bone marrow metaphases were Ph^1-.

Results

The clinical characteristics of the 24 patients with blCML are shown in Table 1. Most patients were Ph^1+ and had been treated previously for an antecedent chronic phase of the disease. The majority of patients were myeloid and/or Tdt negative. All but 6 patients had failed prior treatment for the blastic transformation prior to receiving treatment with mitoxantrone.

Of the 5 patients with Ph^1- blCML or in whom cytogenetics was not available, there was one partial response in a patient with myeloid morphology. Survival in this patient is ongoing at 26 months from the start of his treatment.

Of the 19 patients with Ph^1+ blCML, there were five responses. These occurred in both lymphoid and non-lymphoid transformation. Of the 8 patients with lymphoid transformation, there were two responses. In 1 patient, the post-treatment bone marrow was morphologically normal without evidence of blast crisis (partial response). Follow-up cytogenetic study was not done. Her survival was 8 months from the start of mitoxantrone. In the second responder, the bone marrow was morphologically normal

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Table 1. Mitoxantrone in blCML. Patient characteristics

Sex: Male	12
Female	12
Median age in years (range)	46 (22–72)
Cytogenetics: Ph +	19
: Ph −	3
: Unavailable	2
Tdt (+) or lymphoid	8
Tdt (−) or myeloid	16
Antecedent chronic phase	21
No chronic phase	3
Prior treatment for blCML	18
No prior treatment for blCML	6

and examination of the bone marrow failed to show the Ph^1 chromosome (complete true remission). The patient underwent bone marrow transplantation from a HLA compatible sibling and she relapsed 5 months post-transplant.

Of the 11 patients with non-lymphoid transformation, there was one early death and three responses. The responses included one patient with erythroblastic transformation. Post-treatment marrow was morphologically normal and he lived 5 months from the start of mitoxantrone (cytogenetic study was not done).

The second responder had a post-treatment bone marrow that was no longer diagnostic of blCML and showed 27% Ph^1- metaphases (partial true remission). His survival was 9 months post-initiation of mitoxantrone. In the third patient the post-treatment marrow was normal with 80% Ph^1- metaphases (partial true remission). He died from veno-occlusive disease 2 months after receiving a bone marrow transplant from an HLA-compatible sibling.

Discussion

The purpose of this study was to evaluate the effectiveness of mitoxantrone in treating the blastic phase of chronic myelogenous leukemia. In this trial, we demonstrated modest activity for mitoxantrone in blastic CML. This was seen both in patients whose cells were Tdt+ or lymphoid as well as in patients with Tdt – or myeloid blastic transformation.

Furthermore, patients who had failed previous chemotherapy also responded. Post-treatment survival in the majority of responders was generally brief. Thus, until other more effective alternatives for blCML become available, mitoxantrone should be considered a worthwhile therapeutic option.

Of greater significance was the restoration of Ph^1- hematopoeisis in some responders. True remission of CML occurs rarely with single-agent busulfan [7] and more commonly can be seen with more intensive chemotherapy [8, 9]. Conventional chemotherapy also induces true remission of Ph^1+ Tdt+ acute leukemia [10] and occasionally Tdt− blastic CML. In general, the true remission state is very short lived with repopulation of the Ph^1+ cells usually within 3 to 4 months. Although further intensification of treatment does not appear possible without incurring the risk of increased morbidity and mortality [9], it is possible that some of the newer agents may be more selective against CML.

Mitoxantrone not only can induce remission of blastic CML [3, 4, 5, 11] but also can induce true remission of the disease with reappearance of predominantly Ph^1- cells. This raises the possibility of greater activity against chronic phase CML and provides support for a trial in chronic phase CML with mitoxantrone.

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