Treatment of Myelodysplastic Syndromes with Daily Oral Idarubicin

A Phase I–II Study

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Background. **Idarubicin, a new anthracycline analogue, is available in an oral preparation, and responses have been observed using relatively aggressive therapy in patients with myelodysplastic syndromes (MDS). The authors studied whether a chronic low-dose schedule would be effective but less myelotoxic.**

Methods. **Forty-two patients with MDS received daily low-dose oral idarubicin in 5-week courses that included 3 weeks of treatment, followed by a 2-week rest period. Doses were escalated when possible after the second course, and each patient was to receive six courses.**

Results. **Only one partial response was observed. Although no patient had fatal bone marrow toxicity, only eight patients received the full six courses, primarily because of myelosuppression.**

Conclusions. **This schedule of oral idarubicin is relatively safe but produces fewer responses than are reported with the high-dose pulse regimens. *Cancer* 1993; 71:1989–92.**

Key words: daily oral idarubicin, myelodysplastic syndromes.

The myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal hematopoietic disorders characterized by abnormal cellular maturation that results in ineffective hematopoiesis and often evolution into acute leukemia.[1] Despite numerous clinical trials, the current therapeutic options for these syndromes do not result in sustained improvement in hematopoiesis or postpone the leukemic transformation. Although the hematopoietic growth factors appear promising,[2] our current treatment regimens remain unsatisfactory, other than allogeneic bone marrow transplantation, which can be used in young patients for whom a compatible donor is available.[3]

In general, most patients with MDS are elderly and cannot tolerate aggressive myelotoxic chemotherapy. Occasional responses have been observed with low-dose cytosine arabinoside, but not without great toxicity.[4] It remains to be determined whether this agent is acting by a cytotoxic mechanism, by cellular differentiation, or by both mechanisms. The high incidence of myelosuppression observed is most consistent with a cytotoxic mechanism.

Idarubicin is one of the new anthracycline analogues. Structurally, idarubicin differs from daunorubicin because of the lack of methoxy group in the C4 position of the aglycone.[5] In a variety of murine leukemias and solid tumors, idarubicin has a higher therapeutic index than doxorubicin or daunorubicin.[5] The intravenous preparation has been approved for the treatment of acute nonlymphocytic leukemia. Unlike daunorubicin or doxorubicin, idarubicin is available in an oral preparation, and responses have been observed in patients with acute nonlymphocytic leukemia[6,7] and MDS[8–10] treated with relatively aggressive therapy. Chronic low-dose oral idarubicin therapy also may be effective but less myelotoxic, and thus better tolerated.

The current trial was done to determine if therapy with daily oral idarubicin results in improvement of hematologic parameters in patients with poor prognostic

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MDS. The toxicity of this therapy in this group of patients, who in general are susceptible to myelosuppression, also was studied.

Patients and Methods

Patients

The study population consisted of patients with the following well-established MDS as defined by a modification of the French–American–British classification.[11]

1. Refractory anemia with excess blasts (RAEB).
2. Refractory anemia with excess blasts in transformation (RAEBt).
3. Chronic myelomonocytic leukemia (CMML).
4. Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) with one or more chromosomal abnormalities (other than 5q−) and transfusion of an average of 2 or more units of erythrocytes per month during the preceding 10 weeks.

Patients with primary or secondary MDS were eligible. Patients could not have received cytotoxic chemotherapy or radiation therapy within the 4 weeks before study entry. They could not have received any prior anthracycline or anthracene. At the time of registration, they were not permitted other therapeutic modalities, including hematopoietic growth factors, corticosteroids, androgens, pyridoxine, or vitamin B12. For patients with a diagnosis of RAEB, RAEBt, or CMML, a bone marrow study was required within 2 weeks of patient entry. Additional eligibility criteria included the following:

1. Life expectancy of at least 8 weeks and Eastern Cooperative Oncology Group performance status of 2 or less.
2. Serum bilirubin of 2 mg/dl or less and serum creatinine of 2.0 mg/dl or less.
3. Absence of moderate or excessive myelofibrosis or massive splenomegaly (5 cm or more below left costal margin).
4. Absence of congestive heart failure, uncontrolled ischemic heart disease, significant irreversible arrhythmias, uncontrolled hypertension, myocardial infarction within the previous 6 months, or left ventricular ejection fraction below normal limits.
5. Patients with RAEB were required to have a hemoglobin of less than 10 g% (in absence of transfusions) or absolute granulocyte count of less than $1000/mm^3$ or platelet count of less than $120,000/mm^3$. These restrictions did not apply for patients with RAEBt or CMML.

Treatment Plan

The initial dose of idarubicin for all patients was 2 mg a day orally as a single dose. Antiemetics could be administered at the discretion of the investigator; however, corticosteroids were to be used as an antiemetic only. Their use was discouraged and restricted to the first 24 hours of each course. Each course was 5 weeks (35 days) in duration. Idarubicin was administered daily for the first 21 days of each course. The remaining 14 days were used as a treatment rest period and to evaluate the results of therapy. The patients were to receive at least six courses, each 35 days in duration, unless there was disease progression or significant toxicity. If after two courses (70 days or more), no toxicity was observed that resulted in dose reduction or dose delay, the daily dose of idarubicin for Course 3 was increased to 3 mg/day. If after two additional courses (the third and fourth courses) there had been no objective response or toxicity that resulted in dose reduction or dose delay, the daily dose of the next course (Course 5) was to be increased to 4 mg/day. The dose of 4 mg/day represented the maximum dose any patient could receive. Treatment was held if the platelet count or absolute granulocyte count dropped to less than 50% of the value recorded at entry to the study. Treatment was resumed at 1 mg/day below the previous dose in the absence of bleeding, infection, or other intercurrent illnesses related to therapy, after partial or complete recovery from the nadir count. If there was less than partial recovery in the nadir count on five separate occasions during one course, on the sixth occasion the patient was removed from the study and a bone marrow study done.

The patients were dismissed from the study early for the following reasons: disease progression; unacceptable toxicity; and cardiac events, including the appearance of congestive heart failure or significant fall in the left ventricular ejection fraction defined as 10% or more (absolute) and to below lower limits of normal; absolute decrease of at least 20% from baseline; or a decrease of 5% or more below the lower limits of normal.

The patients were seen before each course of treatment. A complete blood cell count with differential and platelet count was obtained every week, and blood chemistry studies were performed before each course of treatment.

Response Criteria

A complete response was defined as a return of the peripheral blood counts to normal (absolute granulo-

cyte count, more than 2000/mm^3; platelet count, more than 140,000 mm^3; hemoglobin, 12 g% or more) for 10 weeks or longer and a bone marrow aspiration revealing normal erythroid, granulocytic (including less than 5% blasts), and megakaryocytic maturation and absence of transfusions for 10 weeks or longer.

A partial response was defined by any one or more of the following, which appeared after at least 10 weeks on study and lasted for 10 weeks or more: 50% or greater decrease from baseline of erythrocyte transfusion requirement/month (only if the baseline was at least 5 units/10 weeks), increase in hemoglobin level of 2 g/100 ml or more without erythrocyte support, 50% or greater increase from baseline in absolute granulocyte count, or 50% or greater increase from baseline in platelet count (without platelet transfusion support). For patients with CMML, a partial response was defined as 50% or greater decrease from the absolute monocyte count recorded at beginning of the study. Patients with stable disease experienced a regression for 10 weeks or more, which was not significant enough to be classified as a partial response, but had no evidence of progression. Only patients who received at least two cycles (10 weeks) of therapy with appropriate disease assessment were evaluable for efficacy.

Results

Forty-two patients were entered in this study. Two-thirds, or 28, had RAEB; 6, CMML; 3, RA; 1, RARS; and 4, RAEBt. Forty-one patients had primary MDS.

The mean number of courses administered was 2.92, with a median of 2 and a range of 1–7. Three patients received the maximum 4-mg dose. The most common reason for early dismissal from the study was unsatisfactory recovery from myelosuppression (14 patients). In two patients, a fall in the left ventricular ejection fraction was the reason for termination.

Table 1. Response by French-American-British Classification*

FAB classification (no. of patients)	Partial response	Stable disease	Progressive disease	Not evaluable
RAEB (28)	1	16	4	7
CMML (6)	—	1	5	—
RAEBt (4)	—	2	2	—
RA (3)	—	1	—	2
RARS (1)	—	—	1	—

FAB: French-American-British; RAEB: refractory anemia with excess blasts; CMML: chronic myelomonocytic leukemia; RAEBt: refractory anemia with excess blasts in transformatiion; RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts.

* Expressed as no. of patients.

Table 2. Nonhematologic, Noncardiac Toxicities*

Type	Degree†		
	Mild	*Moderate*	*Severe*
Nausea and vomiting	4	3	2
Diarrhea	5	1	1
Anorexia	2	1	2
Alopecia	2	—	2
Stomatitis	1	1	—
Abdominal discomfort	3	1	—
Rash	3	1	—

* Expressed as no. of patients.

† Based on Eastern Cooperative Oncology Group criteria.

Responses

No complete responses were observed. There was only one partial response. A patient with RAEB was observed to have an increase in baseline platelet count (39,000 to 150,000/mm^3) for more than 3 months. Twenty patients had stable disease; 12 had progressive disease; and 9 were not evaluable for response because they did not receive at least two cycles of therapy. Five patients developed acute leukemia, and nine died. The responses by French–American–British classification are listed in Table 1.

Toxicities

Nonhematologic toxicities. In general, idarubicin was well tolerated. The nonhematologic toxicities are shown in Table 2.

Cardiac toxicity. Three patients had a significant decrease in left ventricular ejection fraction, but none had clinical congestive heart failure.

Hematopoietic toxicities. Primarily because of myelosuppression, only eight patients received the full six courses of treatment. Because of myelosuppression, eight patients received fewer than two courses, four received only one course, and four received a portion of the second course. However, no patient experienced fatal marrow toxicity. Of the 14 patients removed from the study prematurely because of myelosuppression, 8 had granulocytopenia, 4 had thrombocytopenia, and 2 had both.

Discussion

It was disappointing to observe that despite the ease of administration and lack of severe toxicity, idarubicin in this dose and schedule of administration was ineffective in the treatment of MDS. This was particularly evi-

dent in the treatment of patients with CMML, for which the assessment of efficacy is less difficult than that in the other MDS. Although we found idarubicin to be associated with fewer side effects than low-dose cytosine arabinoside, it also produced fewer responses.[4] In addition, despite the relatively low doses of idarubicin used, myelosuppression prevented most patients from receiving the prescribed six courses, and eight patients could not complete the first two courses. Additional dose escalations with this chronic daily schedule could have resulted in more severe, if not fatal, myelotoxicity.

It is possible that a different schedule of administration (e.g. higher doses for shorter periods of time), such as that used in some of the European studies would yield better results. Johnson and Parapia[8] reported a 100% response rate in a series of six patients with RAEB (three complete responses; three partial responses) who received a single dose of idarubicin of 50 mg/m^2 orally at 2- or 3-week intervals. However, this regimen produced a hypoplastic bone marrow, and recovery was more delayed with each subsequent course. In addition, 7 of 20 treatment courses were associated with septicemia.

Using a 50-mg dose every 3–4 weeks, Berrebi and Polliack[9] reported three responses in a group of five patients with RAEBt and a response in a patient with sideroblastic anemia who received only a single course of idarubicin. In addition, the toxicity was mild, consisting primarily of nausea, vomiting, lethargy, or mild headache.

In a larger study, DeBock et al.[10] reported two complete responses in a group of 14 patients with RAEB and RAEBt who received 50 mg/m^2 of idarubicin 14 days apart as induction therapy. The response duration was short (median, 3.5 months), and although no nonhematologic toxicities of greater than Grade 2 by World Health Organization standards were observed, two patients had severe fatal aplasia. These authors concluded that idarubicin administered in this method produced comparable antitumor activity to cytosine arabinoside but with less toxicity.

A regimen somewhat more aggressive than our daily low-dose schedule but less intensive than the regimens of Johnson and Parapia[8] or DeBock[10] may yield a reasonable response rate without excessive toxicity. This should be considered for future clinical trials because oral idarubicin has been shown to have activity in MDS.

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