Phase I–II Study of Epirubicin in Multiple Myeloma


ABSTRACT

Forty patients with relapsed (26) or refractory (14) myeloma were treated with epirubicin of doses of 75, 90, 105, and 120 mg/m² in groups of 6 or more patients to test for response, maximum tolerated dose, and toxicity. Thirteen patients had received prior doxorubicin and were included in the dose findings part of the study only. Staging was I (1), II (5), and III (34). Partial responses were seen in 5 patients (18.5%) (duration 1.5, 2, 2.5, 10, and 18 months) not previously treated with doxorubicin. No responses were seen in patients treated with prior anthracycline. Responses were not dependent upon dose level of epirubicin. Median nadir white blood cell count at the four-dose levels were 2,300, 1,000, 600, and 1,700/mm³ with median nadir granulocyte counts of 897, 720, 688, and 192/mm³. Fever/neutropenia was infrequently observed at the three lower dose levels but occurred in 6 of 10 patients at 120 mg/m². Platelet nadirs were 110,000, 83,000, 169,000, and 42,000/mm³. Nonhematological toxicity was not dose dependent and included alopecia (100%), nausea/vomiting (40%), and stomatitis (25%). Six patients had ≥0.10 changes in the resting ejection fraction with one patient developing congestive heart failure that responded to medical management. This patient had received prior doxorubicin and had a history of myocardial infarction.

Epirubicin can produce remissions in patients with previously treated myeloma who have not received prior doxorubicin. Since the response rate was not enhanced at 120/m² and since fever/neutropenia was seen regularly at this dose level, the recommended dose for further study is 105 mg/m².

INTRODUCTION

Epirubicin (4'-epidoxorubicin) is a new anthracyline antibiotic differing from doxorubicin by the epimerization of the hydroxyl group in position 4' of the amino sugar moiety. Its mechanism of action is similar to that of doxorubicin and its antitumor activity appears to be comparable, mg for mg. However, the therapeutic index is more favorable for epirubicin (1) with less hematological and cardiac toxicity at equivalent doses (2). Recently, a review has presented the experience with epirubicin in a wide variety of tumors (3).

The following trial was established to evaluate the maximum tolerated dose and efficacy in previously treated patients with multiple myeloma.

MATERIALS AND METHODS

Requirements for entry into this protocol included: patients with multiple myeloma who had relapsed or failed at least one prior program of chemotherapy; performance status 0–2 (Eastern Cooperative Oncology Group); ≥18 years old, life expectancy ≥12 weeks; recovery from toxic effects of prior chemotherapy or radiotherapy; WBC, ≥4,000/mm³; platelet count, ≥100,000/mm³; bilirubin, ≤2.0 mg/100 ml; creatinine, ≤2.0 mg/100 ml; calcium, ≤11 mg/dl; alkaline phosphatase, ≤2× upper limit of normal; SGOT/SGPT ≤2× upper limit of normal; absence of decompensated heart failure; radionuclide ejection fraction, ≥10% below the normal value for institution; absence of a second active malignancy; and informed consent. Patients with abnormal hematological values were considered eligible if these abnormalities were related to myeloma. Patients who had received ≤250 mg/m² doxorubicin were eligible to be entered into the Phase I dose-finding part of the protocol (see below). Pretreatment evaluation included history, physical examination, performance status, height, and weight. Laboratory procedures were: complete blood count with platelet count; segmental multianalyzer survey including blood urea nitrogen, creatinine, uric acid, bilirubin, SGOT, SGPT, alkaline phosphatase, protein and immunoglobulin assay of serum and urine (24-h sample); bone marrow aspiration with biopsy; skeletal survey; electrocardiograph; and radionuclide ejection fraction.

To assess response, myeloma protein studies of serum and urine were repeated before each cycle. In patients with documented lytic lesions or fractures, response was confirmed with follow-up X-rays to evaluate size and number of lytic bone lesions or severity of osteoporosis or fractures. Complete blood counts with platelet counts were performed weekly and chemistries were repeated every 3 weeks to evaluate toxicity. Cardiac function was assessed by determination of the resting radionuclide ejection fraction prior to the first cycle of therapy and was repeated every 3–4 cycles and off study. Significant changes in the ejection fraction were defined according to the criteria of Alexander et al. (4).

A complete remission was defined by the disappearance of the myeloma protein in serum/urine on two consecutive measurements 4 weeks apart, associated with healing of bone lesions. A PR was defined as a ≥50% reduction in the serum myeloma protein level and/or 75% reduction in the 24-h urine M-component level on two consecutive measurements 4 weeks apart. These responses must also be associated with the absence of hypercalcemia, new bone lesions, and/or any evidence of progressive/new disease. The maximum tolerated dose was defined as the dose level that required dose reductions in the majority of patients treated with that dose because of toxicity.

Epirubicin was supplied by Adria Laboratories (Division of Erba-mont, Inc., Columbus, OH) as a red-orange crystalline powder in vials containing 10 or 50 mg of 4'-epidoxorubicin hydrochloride. It was reconstituted in sterile water or saline for injection in a concentration of 2 mg/ml and administered i.v. over 30 min.

The initial dose of epirubicin in this study was 75 mg/m². Therapy was repeated every 3 weeks provided there was adequate bone marrow recovery, granulocyte count ≥1,500/mm³, WBC ≥4,000/mm³, and platelets ≥100,000/mm³ or granulocytes/platelets ≥ starting level. Three patients were initially treated at this dose level; an additional three or more patients were entered at this dose level after toxicity was defined. Groups of six or more patients were then to be entered at the 15-mg/m² increments (90 mg/m², 105 mg/m², 120 mg/m², etc.) pending toxicity, until the maximum tolerated dose was defined. Patients who had received prior doxorubicin were eligible for the dose-escalating toxicity aspects of the study but were considered separately in determining response. Dose adjustments were made according to the following schedule: (a) if day 22 WBC ≤4,000 and platelets ≥100,000, epirubicin increased by 10 mg/m² for nadir WBC ≤2,000/mm³ and platelets ≥70,000/mm³ but same dose maintained if nadir WBC ≤2,000/mm³ and platelets ≤70,000/mm³; (b) if day 22 WBC 2,000–3,999/mm³, and platelets 50,000–99,999/mm³, dose reduced by 10 mg/m² after marrow recovery; (c) if day 22 WBC ≤2,000/mm³ and platelets ≤50,000/mm³, epirubicin reduced dose by 20 mg/m² after marrow recovery. Therapy...
was discontinued if the ejection fraction fell by \( \geq 0.10 \).

Responding patients (complete remission and PR) received therapy for one year or until progression. Patients who developed progressive disease after two cycles (or after one cycle if rapid progression) or who failed to achieve at least a PR after three courses were considered treatment failures and taken off study. All patients starting therapy were considered evaluable.

Characteristics of patients participating in this study are summarized in Table 1. Primary treatment programs in these patients included: M-2 [1,3-bis(2-chloroethyl)-1-nitrosourea, cyclophosphamide, vincristine, melphalan, and prednisone] [16 patients]; melphalan and prednisone [13 patients]; high-dose melphalan [7 patients]; interferon, melphalan, and prednisone [2 patients]; and vincristine, Adriamycin, and dexamethasone [2 patients]. Programs utilized in second-line therapy included M-2, interferon, interferon and doxorubicin, doxorubicin, and vincristine, Adriamycin, and dexamethasone. Patients who were progressive on prior therapy were considered "refractory"; patients who failed to achieve at least a PR after three courses were considered "relapsing."

RESULTS

The responses to epirubicin in myeloma are illustrated in Table 2. Patients without prior doxorubicin were evaluated for response. The patients who had received doxorubicin were evaluated for toxicity only. All patients who started therapy were considered evaluable. The response rate was 18.5% (5 of 27) (95% confidence limits, 4–33%) in patients who had not received doxorubicin. No responses were seen in the group of patients who had received prior doxorubicin. All responses were PR; however, one patient (PR, 18 months) had normalization of immunoglobulins, disappearance of paraprotein, and normalization of the bone marrow but failed complete remission criteria because of the lack of healing of bone lesions. Responses were seen only in patients who had received only one prior treatment regimen. Four of the responses occurred in patients who had responded to prior chemotherapy; only one patient responded who was progressive on prior therapy and could be considered "refractory." There was no correlation between prior response, the specific prior treatment program, stage, or paraprotein. One patient with Stage I disease was treated on this study because of a rapid rise in paraprotein.

Responses appeared independent of the dose levels used in this study: 1 of 2 at 75 mg/m², 3 of 14 at 90 mg/m², 0 of 3 at 105 mg/m², and 1 of 7 at 120 mg/m². However, the number of patients treated at each dose level was not sufficient to detect statistical differences in response rates. Moreover, responses were not related to total dose received.

The hematological toxicity is summarized in Table 3. Granulocytopenia was more severe at each higher dose level. The majority of patients at 120 mg/m² developed fever during the first course of therapy, requiring hospitalization and broad-spectrum antibiotics; all patients recovered without sequelae. The number of patients requiring dose adjustments for neutropenia during the first cycle of therapy was similar between dosage levels because dose adjustments were made according to a total WBC. Maximum myelosuppression occurred 7–14 days after therapy, with recovery of peripheral counts by day 21 in the majority of patients. Thrombocytopenia was not as marked as granulocytopenia, except at 120 mg/m².

Nausea/vomiting and stomatitis were seen in the minority of patients and were mild or moderate (Grade I or II) (Table 4). These symptoms were not dose level dependent. The nausea/vomiting was controllable with antiemetics. No patient refused therapy because of this toxicity. Alopecia was universal.

Cardiac function was monitored by regular determinations of the resting radionuclide EF (4). Thirteen of the 40 patients in this study has received prior doxorubicin. The median change in EF was 0.65–0.61 in patients without prior doxorubicin and 0.66–0.59 in the patients with prior doxorubicin. Median dose of doxorubicin in patients previously treated was 100 mg/m².

Table 5 lists the effects on cardiac function noted in this study. Six patients had significant changes in the resting EF (4). These changes were mild (\( \geq 0.10 \)) in five patients, one of which had received prior doxorubicin. One patient developed clinical congestive heart failure. This patient had a prior history of a myocardial infarction and had priory therapy with doxorubicin. The patient was treated with digoxin and furosemide and recovered without sequelae. The median ages of the patient with and without EF changes were similar and there were no differences in prior cardiac history between the groups of patients.

DISCUSSION

Doxorubicin has been utilized in multiple myeloma as a single agent (5), as part of multidrug therapy in relapsed/refractory patients (6, 7), and as part of combination programs in initial therapy (8, 9). Because of its favorable therapeutic index compared with doxorubicin (3), epirubicin was selected for this Phase I–II study in multiple myeloma.

In this study, patients were able to tolerate doses comparable to solid tumor trials (75–90 mg/m²) without excessive hematological toxicity despite marrow disease. Only at 120 mg/m²
did the majority of patients in this study develop fever/neutropenia. In the original phase II trial of doxorubicin in myeloma, patients appeared to have tolerated relatively low-dose doxorubicin (25 mg/m²) less well (5) than the higher doses of epirubicin in this study. Comparative studies should be considered to determine whether higher comparable doses of the newer anthracycline can be delivered to patients with myeloma and whether any dosing difference might have an impact on response.

Stomatitis and nausea/vomiting were seen in the minority of patients which is comparable to the incidence seen in other studies with epirubicin. Cardiac studies were done regularly in patients in this study. There was no significant change in the resting EF for the 40 patients as a group during this study. Five patients in this study had changes consistent with mild cardiac toxicity (≥0.10 change); such effect is not predictive of heart failure (4). Only one patient developed clinical congestive heart failure in the setting of prior cardiac history and doxorubicin exposure. Prior studies have shown that epirubicin may be 50% less cardiotoxic than doxorubicin (10–12). Comparative studies of epirubicin and doxorubicin will be required to define any differential in incidence of cardiac toxicity.

The data in this study suggest that epirubicin is an active agent in previously treated patients with myeloma, with reasonable toxicity. The doses of 75–120 mg/m² were tolerated with acceptable hematological and nonhematological effects, except for the degree of granulocytopenia and the incidence of fever/neutropenia at the highest dose level. Further studies should be considered in multiple myeloma to assess the potential role of this anthracycline in this disease. Comparative studies with doxorubicin will be required to establish any advantage in terms of response and toxicity between these two anthracyclines.

### Table 3 Hematological toxicity of epirubicin

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>Median nadir WBC/mm³ (range)</th>
<th>Median nadir granulocyte count/mm³ (range)</th>
<th>Median nadir platelet count/mm³ (range)</th>
<th>No. of patients requiring dose reductions because of hematological toxicity</th>
<th>No. of patients having episodes of fever/neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>2.300 (1.900–2.800)</td>
<td>897 (608–2.240)</td>
<td>110,000 (88,000–189,000)</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>90</td>
<td>1.000 (300–2.400)</td>
<td>720 (16–1.015)</td>
<td>83,000 (18,000–141,000)</td>
<td>7/17</td>
<td>3/17</td>
</tr>
<tr>
<td>105</td>
<td>1.600 (1,100–5,400)</td>
<td>688 (210–3.456)</td>
<td>169,000 (31,000–177,000)</td>
<td>2/7</td>
<td>1/7</td>
</tr>
<tr>
<td>120</td>
<td>1.700 (100–2,300)</td>
<td>192 (0–400)</td>
<td>42,000 (5,000–158,000)</td>
<td>4/10</td>
<td>6/10</td>
</tr>
</tbody>
</table>

* First course of therapy at each dose level.

### Table 4 Nonhematological toxicity of epirubicin

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia*</td>
<td>40 (100)*</td>
</tr>
<tr>
<td>Nausea/vomiting* (Grade I or II)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Stomatitis* (Grade I or II)</td>
<td>10 (25)</td>
</tr>
</tbody>
</table>

* Not related to dose levels. Numbers in parentheses, percentage.

### Table 5 Cardiac effects of epirubicin

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Change in EF</th>
<th>Total dose of epirubicin received (mg/m²)</th>
<th>Prior total dose of doxorubicin (mg/m²)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>0.51–0.36</td>
<td>383</td>
<td>100</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>69</td>
<td>0.66–0.51</td>
<td>360</td>
<td>175</td>
<td>No symptoms</td>
</tr>
<tr>
<td>81</td>
<td>0.69–0.56</td>
<td>735</td>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>60</td>
<td>0.52–0.42</td>
<td>454</td>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>72</td>
<td>0.69–0.52</td>
<td>210</td>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>62</td>
<td>0.68–0.52</td>
<td>480</td>
<td>0</td>
<td>No symptoms</td>
</tr>
</tbody>
</table>

**REFERENCES**

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