Phase I–II Trial of High-Dose Epirubicin in Patients with Lymphoma

Delwyn C. Case, Jr., Richard Gams, Thomas J. Ervin, Marjorie A. Boyd, and Fred B. Oldham

INTRODUCTION

High-dose doxorubicin has shown considerable activity in both previously treated and previously untreated patients with lymphoma. Because of the toxicities of doxorubicin at high dose, we elected to study a new anthracycline at doses comparable to doxorubicin at high dose, to assess response and toxicity. Epirubicin was administered at doses of 120 mg/m², 150 mg/m², and 180 mg/m² every 3 weeks (maximum four doses) to groups of six patients with previously treated intermediate- and high-grade lymphoma. Sixteen of the patients had received significant prior therapy with an anthracycline and/or antracyclen. At all dose levels, myelosuppression was severe, with median granulocyte nadirs <500/mm³. Hematological recovery occurred by day 21 at the 120 mg/m² and 150 mg/m² dose levels, allowing for the next cycle of therapy. However, at the 180 mg/m² dose level, the majority of patients failed to have hematological recovery by the day of the next scheduled therapy. Forty-two per cent of patients (eight patients) had fever/neutropenia, and required antibiotics. One treatment-related septic death occurred (at 150 mg/m²). Alopecia (68%), fever immediately following treatment (63%), mild/moderate stomatitis (58%), and nausea/vomiting (53%) were the most common nonhematological toxicities. These toxicities were independent of the dose levels and were not dose limiting. A significant change (>=0.10) in the radionuclide ejection (EF) was seen in seven patients. The median of the entire group of patients fell from 0.63 to 0.56. No patient developed clinical or radiological evidence of congestive heart failure. A response rate of 58% (two complete responses, nine partial responses) was achieved with a median duration of 5 months (range, 1–154).

High-dose epirubicin can be successfully utilized in patients with previously treated lymphoma. The only dose-limiting toxicity observed at these dose levels was the lack of hematological recovery by day 21 with 180 mg/m². Since epirubicin at high dose will be incorporated into high-dose anthracycline regimens in previously untreated patients utilizing a 3-week treatment cycle, 150–180 mg/m² may be the maximally tolerated dose for such treatment cycles.

ABSTRACT

High-dose doxorubicin has shown considerable activity in both previously treated and previously untreated patients with lymphoma. Because of the toxicities of doxorubicin at high dose, we elected to study a new anthracycline at doses comparable to doxorubicin at high dose, to assess response and toxicity. Epirubicin was administered at doses of 120 mg/m², 150 mg/m², and 180 mg/m² every 3 weeks (maximum four doses) to groups of six patients with previously treated intermediate- and high-grade lymphoma. Sixteen of the patients had received significant prior therapy with an anthracycline and/or antracyclen. At all dose levels, myelosuppression was severe, with median granulocyte nadirs <500/mm³. Hematological recovery occurred by day 21 at the 120 mg/m² and 150 mg/m² dose levels, allowing for the next cycle of therapy. However, at the 180 mg/m² dose level, the majority of patients failed to have hematological recovery by the day of the next scheduled therapy. Forty-two per cent of patients (eight patients) had fever/neutropenia, and required antibiotics. One treatment-related septic death occurred (at 150 mg/m²). Alopecia (68%), fever immediately following treatment (63%), mild/moderate stomatitis (58%), and nausea/vomiting (53%) were the most common nonhematological toxicities. These toxicities were independent of the dose levels and were not dose limiting. A significant change (>=0.10) in the radionuclide ejection (EF) was seen in seven patients. The median of the entire group of patients fell from 0.63 to 0.56. No patient developed clinical or radiological evidence of congestive heart failure. A response rate of 58% (two complete responses, nine partial responses) was achieved with a median duration of 5 months (range, 1–154).

High-dose epirubicin can be successfully utilized in patients with previously treated lymphoma. The only dose-limiting toxicity observed at these dose levels was the lack of hematological recovery by day 21 with 180 mg/m². Since epirubicin at high dose will be incorporated into high-dose anthracycline regimens in previously untreated patients utilizing a 3-week treatment cycle, 150–180 mg/m² may be the maximally tolerated dose for such treatment cycles.

INTRODUCTION

Studies performed with animal models have shown that the efficacy of high-dose therapy in sensitive human tumors such as the lymphomas and small cell lung cancer is increased a 3-week treatment cycle, 150–180 mg/m² may be the maximally tolerated dose for such treatment cycles.

ABSTRACT

Epirubicin (4'-epidoxorubicin) is a new anthracycline antibiotic differing from doxorubicin by the epimerization of the hydroxyl group in position 4' of the aminosugar moiety. Its mechanism of action is similar to that of doxorubicin and its antitumor activity appears to be comparable, milligram for milligram. However, the therapeutic index is more favorable for epirubicin (5), with less hematological and cardiac toxicity at equivalent milligram doses (6). Significant responses have been seen in lymphomas with a 55% response rate recently reported in a phase II study at a dose of 90 mg/m³ (7). The present trial was devised to establish the maximum tolerated dose of high-dose epirubicin and to examine whether high-dose epirubicin could produce the same favorable results but with less toxicity in previously treated patients with non-Hodgkin's lymphoma seen with high-dose doxorubicin.

MATERIALS AND METHODS

Requirements for entry into this protocol included histological confirmation of intermediate or high-grade non-Hodgkin's lymphoma (working formulation) (8) or the following types of lymphoma by the Rappaport Classification (9): nodular histiocytic lymphoma, diffuse poorly differentiated lymphocytic lymphoma, diffuse mixed lymphoma, diffuse histiocytic lymphoma and diffuse undifferentiated lymphoma, prior combination chemotherapy, performance status (0–3) (Eastern Cooperative Oncology Group), age >=15 years old, bidimensionally measurable disease, WBC >=3,000/mm³ and platelet count >=100,000/mm³ (unless there was bone marrow involvement), bilirubin <=1.3 mg%, prior doxorubicin <=450 mg/m², resting radionuclide ejection fraction >=0.50, and written informed consent.

Pretreatment evaluation included history, physical examination, performance status, weight, height, and tumor measurements. Laboratory procedures were complete blood count with platelet count, urinalysis, Sequential Multi-Analyzer (SMA) survey (blood urea nitrogen, creatinine, uric acid, bilirubin, serum glutamic oxaloacetic transaminase, and alkaline phosphate), electrocardiogram, chest X-ray, chest and abdominal computerized axial tomography or lymphangiogram, bone marrow biopsy, and radionuclide ejection fraction.

Clinical and radiographic studies were repeated after each 3-week cycle to define response. 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 dose of high-dose epirubicin and was repeated after each cycle of therapy. Significant changes in the ejection fraction were defined according to Alexander et al. (10).

A CR was defined as the clinical and X-ray disappearance of all detectable disease for a minimum of 4 weeks without the appearance of any new lesions. A PR was defined as a 50% or greater reduction in the sum of the products of the maximal perpendicular diameters of all measurable lesions for at least 4 week without the appearance of any new lesions. The MTD was considered to have been exceeded when >50% of patients entered at a generic dose level failed to achieve unequivocal hematological recovery values [WBC >=3,000/mm³ (granulocytes >=1,500/mm³) and platelet count >=100,000/mm³] 21 days after therapy.

The abbreviations used are: CR, complete remission; PR, partial remission; MTD, maximal tolerated dose; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; M-BACOD, methotrexate-bleomycin-doxorubicin-cyclophosphamide-vincristine-dexamethasone; MOPLACE, methotrexate-vincristine-prednisone-leukovorin-cytosine arabinoside-etoposide; EF, ejection fraction.

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Epirubicin was supplied by Adria Laboratories (Division of Erbafort, 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 for injection or saline to a concentration of 2 mg/ml and administered i.v. over 30 min.

The initial dose of epirubicin in this study was 120 mg/m² i.v. Therapy was repeated every 3 weeks provided there was adequate bone marrow recovery [granulocyte count ≥ 1,500/mm³ (WBC ≥ 3,000/mm³) and platelets ≥ 100,000/mm³]. Three patients were initially treated at this dose; an additional three patients were entered at this dose level after toxicity was defined. Groups of six patients were then to be entered at 30 mg/m² increments (150 mg/m², 180 mg/m², etc.) pending subsequent courses.

Responding patients (CR ± PR) received four courses of therapy. Patients who developed progressive disease after one cycle or who failed to achieve at least a PR after two courses were regarded as treatment failures and taken off the study. All patients starting therapy were considered evaluable.

Characteristics of patients participating in this study are summarized in Table 1. All had received prior initial therapy which included multidrug combination chemotherapy: CHOP, M-BACOD, or methotrexate-vincristine-prednisone-leukovorin-cytosine arabinoside-etsopside-CHOP. Only three patients (with diffuse poorly differentiated lymphocytic lymphoma) had not received prior anthracycline/anthracenedione therapy: cyclophosphamide-vincristine-prednisone and carbustine-cyclophosphamide-vincristine- melphalan-prednisone. Mitoxantrone was utilized as part of the M-BACOD program or as a single agent for relapsing disease. Aclacinomycin was utilized as a single agent for relapsing lymphoma.

RESULTS

The hematological toxicity is summarized in Table 2. Neutropenia/granulocytopenia was severe with progressive myelosuppression at the higher dose levels of high-dose epirubicin. Maximum myelosuppression occurred 7–14 days after therapy. Recovery of peripheral counts occurred by day 21 in patients at the 120 and 150 mg/m² levels. However, the majority of patients at 180 mg/m² of high-dose epirubicin required delay of therapy because of prolonged recovery from myelosuppression to days 28–35. Thrombocytopenia was not as marked as the granulocytopenia. The duration and degree of myelosuppression did not increase with subsequent courses of therapy. Eight patients developed febrile episodes (oral temperature > 38.3 presumed to be of infectious etiology). Each received broad spectrum antibiotics. One patient died during an infectious episode despite antibiotic treatment; this patient also suffered a myocardial infarction and ventricular fibrillation during the hospitalization as well as other signs of multiorgan failure. Nausea and vomiting, fever (immediately post therapy), and alopecia were seen in the majority of patients and were not related to dose (Table 3). The nausea and vomiting was controllable with antiemetics. No patient refused therapy because of this toxicity. Stomatitis, usually mild (1+) or moderate (2+), was seen in 11 patients and was more common at the higher dose levels. Severe (3+) stomatitis was seen in four patients; three at the 150 mg/m² and another at the 180 mg/m² dose levels. The severity did not increase with subsequent courses.

The objection responses to high-dose epirubicin are illustrated in Table 4. All patients were considered evaluable. The response rate to high-dose epirubicin in these 19 patients was 58%. There was no significant difference in response between the three dose levels utilized in this study. However, the number of patients treated at each dose level was not sufficient to permit detecting differences in response rates. Responses were seen both in relapsing patients (10/14) and in refractory patients (1/5). The dose of prior anthracycline/anthracenedione was comparable between the responders and nonresponders. Two patients in this study (all responders) had not received prior anthracycline and/or anthracenedione. In patients receiving prior anthracyclines and/or anthracenedione the response rate was 56%. Responses were seen in each lymphoma histological subtype. A median of three courses of epirubicin (range 1–4) was administered to patients.

Cardiac function was monitored by regular determinations of the resting radionucleide EF (10). Sixteen of the 19 patients in this study had received prior anthracycline and/or anthracenedione. The median change in the EF was 0.63 to 0.56 for the entire group of patients during therapy. The median prior doses of anthracycline/anthracenedione in the 12 patients who

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Hematologic toxicity of high-dose epirubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>Nadir WBC (range)</td>
</tr>
<tr>
<td>120 mg/m²</td>
<td>1,400/mm³</td>
</tr>
<tr>
<td>150 mg/m²</td>
<td>1,300/mm³</td>
</tr>
<tr>
<td>180 mg/m²</td>
<td>400/mm³</td>
</tr>
</tbody>
</table>

* Not related to dose level.
did not demonstrate significant changes in the EF were: doxorubicin (300 mg/m²), mitoxantrone (100 mg/m²), and aclacinomycin (320 mg/m²). In the seven patients who had significant EF changes, the prior doses were: doxorubicin (240–403 mg/m²), mitoxantrone (57.5 mg/m²), and aclacinomycin (100 mg/m²).

Table 5 lists the effects on cardiac function noted in this study. The median dose of epirubicin received by the patients who had no significant cardiac changes was 360 mg/m² (range, 300–720) and 360 mg/m² (150–540), in the seven patients who had cardiac changes. There were no episodes of congestive heart failure. The EF changes were either mild (≥0.10; six) or moderate (≥0.15, one) by the criteria of Alexander et al. (10). Only one patient with significant changes in the EF had not received any prior potentially cardiotoxic drugs. This patient had mild changes (0.71–0.55) with a final EF within the normal range. The patient did not have any cardiac risk factors. The median age in the group without cardiac changes was 67 and 71 years in the patients with EF changes.

Acute cardiac symptomatology developed in three patients during infection during neutropenic states. In two patients, the symptoms resolved when the active infection resolved. Both patients received additional courses of high-dose epirubicin without recurrence of these cardiac symptoms. In the third patient, disease-induced multisystem failure developed and the patient expired.

DISCUSSION

Recent studies utilizing combination chemotherapy for the intermediate and high-dose non-Hodgkin’s lymphomas have shown high complete response rates. The remissions in the majority of patients achieving complete remission have been durable (11). Because of this success, several studies have been initiated utilizing intensive chemotherapy over a shorter duration (4, 12). One such approach has used high-dose doxorubicin in combination with vincristine, prednisone, cyclophosphamide, and cytosine arabinoside (4), based upon prior Phase II reports demonstrating a high response rate to high-dose doxorubicin in both lymphoma (six responders in seven patients) (2) and solid tumors (3). In these Phase II studies, repeated courses of doxorubicin 120 mg/m² could be given with manageable toxicities. Myelosuppression was severe with a median granulocyte nadir of <500/mm³ and a median platelet nadir of 67,000/mm³. Stomatitis was seen in 65–85% of patients. Cardiotoxicity was uncommon. These studies suggested a steep dose-response curve for doxorubicin. In the group of previously untreated patients with lymphoma treated with high-dose doxorubicin in combination with other chemotherapeutic agents, an 82% complete response was achieved with projected survival at 4 years of 71% . Myelosuppression was severe and mucositis was seen in 50% of patients. There was no report of cardiac toxicity in these patients (4).

Because of its favorable therapeutic index compared with doxorubicin (13) and its significant activity in lymphoma at conventional Phase II doses (7), epirubicin was selected for study in this protocol to determine whether equivalent doses of high-dose epirubicin would have less toxicity than doxorubicin. In the present group of pretreated patients with intermediate or high-grade lymphoma, it appears that the 150–180 mg/m² levels may be the MTD because of the delay of hematological recovery by 21 days. Since our plans are to incorporate high-dose epirubicin into combination therapy in a regimen of 21-day cycles, it would be advantageous to utilize the maximum dose that would allow full recovery by 21 days to allow continued cycling of drugs. Except for the delay in therapy required at the highest dose levels, other evidence of dose-limiting toxicities was not observed. Myelosuppression was severe at the three dose levels studied and was progressively more severe at the higher doses. Only one death occurred during a period of sepsis/neutropenia in a patient receiving 150 mg/m². In seven other patients, fever/neutropenia occurred, and antibiotics were not effective.

Table 4 Responses to high-dose epirubicin

<table>
<thead>
<tr>
<th>Patient number</th>
<th>CR: 5, 15+ months</th>
<th>PR: 1, 1.5, 1.5, 2, 3, 7, 12, 12+, 14+ months</th>
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<tbody>
<tr>
<td>CR: 5, 15+ months</td>
<td>5/6</td>
<td>150 mg/m² (2/7)</td>
</tr>
<tr>
<td>PR: 1, 1.5, 1.5, 2, 3, 7, 12, 12+, 14+ months</td>
<td>4/6</td>
<td>1180 mg/m² (1/1)</td>
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</table>

Prior anthracycline/anthracenedione therapy

<table>
<thead>
<tr>
<th>Responder</th>
<th>Doxorubicin</th>
<th>Mitoxantrone</th>
<th>Aclacinomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>403 mg/m²</td>
<td>100 mg/m²</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Phases</td>
<td>240–450</td>
<td>42–160</td>
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</tbody>
</table>

Responses according to prior therapy

<table>
<thead>
<tr>
<th>Patient number</th>
<th>No prior anthracylines/anthracenedione</th>
<th>Prior doxorubicin</th>
<th>Prior mitoxantrone</th>
<th>Prior doxorubicin and mitoxantrone</th>
<th>Prior mitoxantrone, doxorubicin, and aclacinomycin</th>
<th>Prior mitoxantrone and aclacinomycin</th>
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<tbody>
<tr>
<td>Age</td>
<td>67</td>
<td>71</td>
<td></td>
<td></td>
<td>1/1</td>
<td>1/5</td>
</tr>
<tr>
<td>EFS</td>
<td>0.71–0.55</td>
<td></td>
<td></td>
<td></td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2/3</td>
<td>2/4</td>
<td>5/5</td>
<td>1/5</td>
<td>0/1</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Table 5 Observed cardiac effects of high-dose epirubicin

<table>
<thead>
<tr>
<th>Ejection fraction (EF)</th>
<th>Patient number</th>
<th>Age</th>
<th>Change in EF</th>
<th>Dose level epirubicin (total dose received)</th>
<th>Prior doxorubicin</th>
<th>Prior mitoxantrone</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45 years</td>
<td>0.49–0.39</td>
<td>120 mg/m² (240 mg/m²)</td>
<td>450 mg/m²</td>
<td>42 mg/m²</td>
<td>No symptoms</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>71 years</td>
<td>0.54–0.44</td>
<td>120 mg/m² (120 mg/m²)</td>
<td>270 mg/m²</td>
<td>100 mg/m²</td>
<td>No symptoms</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>66 years</td>
<td>0.54–0.44</td>
<td>120 mg/m² (480 mg/m²)</td>
<td>0</td>
<td>100 mg/m²</td>
<td>No symptoms</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>72 years</td>
<td>0.71–0.55</td>
<td>150 mg/m² (600 mg/m²)</td>
<td>0</td>
<td>0</td>
<td>No symptoms</td>
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<tr>
<td>11</td>
<td>76 years</td>
<td>0.66–0.50</td>
<td>150 mg/m² (300 mg/m²)</td>
<td>240 mg/m²</td>
<td>0</td>
<td>No symptoms</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>72 years</td>
<td>0.85–0.67</td>
<td>180 mg/m² (720 mg/m²)</td>
<td>0</td>
<td>57.5 mg/m²</td>
<td>No symptoms</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>53 years</td>
<td>0.54–0.38</td>
<td>150 mg/m² (450 mg/m²)</td>
<td>403 mg/m²</td>
<td>94 mg/m²</td>
<td>No symptoms</td>
<td></td>
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</table>

Acute cardiac symptomatology

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patient number</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td>8</td>
<td>Occurred during fever/neutropenia, then resolved</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>11</td>
<td>Occurred during fever/neutropenia, then resolved</td>
</tr>
<tr>
<td>Acute myocardial infarction with ventricular fibrillation</td>
<td>14</td>
<td>Occurred during sepsis/neutropenia, patient expired</td>
</tr>
</tbody>
</table>
utilized. Stomatitis was manageable and may be less frequent and less severe than is generally reported with high-dose doxorubicin (2–4). Although fever within 24 h has been reported with conventional doses of epirubicin (14, 15), the incidence appears substantially higher in this study (63%) and may be related to the high doses of epirubicin utilized. The fever responded to treatment with acetaminophen and resolved within hours.

The incidence of cardiomyopathy may become a factor in the choice of anthracyclines in clinical trials, especially in diseases such as the intermediate and high-grade lymphomas where a high cure rate is emerging. Epirubicin does not produce a significant increase in cardiac endogenous lipoperoxidation as compared with doxorubicin as demonstrated in experimental animals (16). This difference in metabolic effect in the heart may be the result of a difference in tissue distribution between epirubicin and doxorubicin. At equivalent doses of these two anthracyclines, epirubicin has lower tissue concentration as a result of more rapid plasma clearance and a unique glucuronidation pathway (17, 18). In prior studies with equal milligram doses of doxorubicin, epirubicin appears approximately 50% less cardiotoxic than doxorubicin (19–21). Cardiotoxicity evaluation in high-dose doxorubicin trials has been limited. However, compared to the one trial utilizing high-dose doxorubicin where cardiac studies (ejection fractions) were performed, the median change in the EF in our study (0.63–0.56) was less than observed with high-dose doxorubicin (0.71–0.57) (3). Furthermore, only two of 27 patients in the high-dose doxorubicin study had received any prior doxorubicin; in our trial, 16 of 19 patients had received prior anthracycline and/or anthracenedione. Comparative trials will be necessary to delineate differences in cardiotoxicity between epirubicin and doxorubicin at conventional and high doses.

High-dose epirubicin can be administered to previously treated patients with lymphoma and produce a significant response rate. The doses in this study are comparable to those utilized in high-dose doxorubicin trials. We intend to incorporate epirubicin at 180 mg/m² into a combination program analogous to a high-dose doxorubicin trial (4) in previously untreated patients with intermediate and high-grade lymphoma.

REFERENCES

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