Activity of Esorubicin in Recurrent Malignant Lymphoma: A Southwest Oncology Group Study

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A phase II trial of esorubicin (4′ deoxydoxorubicin) was conducted by the Southwest Oncology Group in 88 assessable patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) at the time of first relapse. Esorubicin was administered at two dose levels: 25 mg/m² for patients at risk for excessive myelosuppression, and at 30 mg/m² for all others at 21-day intervals. Overall, 33 of 88 patients (38%) responded to treatment including three complete remissions (CRs; 3%) and 30 partial remissions (PRs; 34%), with the median duration of response lasting 6.2 months. Response rates did not differ significantly by histologic subtype: 31% of 26 patients with favorable NHL, 33% of 43 patients with unfavorable NHL, and 58% of 19 patients with HD. Twelve of 33 responding patients (36%) had relatively durable remissions lasting from 1 to more than 4 years. Leukopenia (< 3,000 cells per microliter) was seen in 65 of 88 patients (74%) and was severe (< 1,000 cells per microliter) in 20 of 88 patients (23%). Clinical signs or symptoms of congestive heart failure were not seen and the ejection fraction (EF) fell 10% to 20% in three patients. Esorubicin is an active agent in patients with NHL or HD at the time of first relapse.

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THE RESULTS of numerous pilot studies conducted over the past 10 years indicate that the proportion of patients cured of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) may have increased with the formulation of new doxorubicin-containing combination chemotherapy regimens.[1-3] However, a high proportion of patients relapse following initial chemotherapy and eventually die of drug-resistant disease.[4-7] Even high-dose chemotherapy with autologous bone marrow rescue is ineffective for the majority of relapsing patients with either NHL or HD.[8] Currently, there is no predictably effective second-line (salvage) therapy for these patients.

Esorubicin (4′ deoxydoxorubicin) is an anthracycline analog synthesized by reduction of the 4′ hydroxyl group on the aminosugar of doxorubicin.[9] Preclinical studies demonstrated esorubicin to be at least as active as doxorubicin against a wide range of tumors using both in vivo murine models and in vitro human clonogenic assays.[10-17] Furthermore, esorubicin was shown to be more than twice as potent as doxorubicin, using an in vitro human tumor clonogenic assay system.[17] In as much as cardiac toxicity correlates with peak plasma anthracycline concentration, the increased potency of esorubicin at lower plasma concentrations appears to offer a cardiac-sparing advantage. Preclinical direct comparison studies using a cardiac toxicity model demonstrated that esorubicin caused few or no cardiac lesions histologically.[10]

Thus, esorubicin was tested in a phase II clinical trial in patients with recurrent NHL lymphoma and HD to establish its activity as second-line therapy.

PATIENTS AND METHODS

Patient Selection

Patients with a histologic diagnosis of malignant lymphoma, including HD and NHL, were eligible for this study. All patients had received previous treatment, but prior chemotherapy exposure was limited to the following definitions. Eligible patients with HD had received prior treat-

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ment with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or a MOPP-ABV hybrid combination. Patients with unfavorable histologies of NHL (intermediate- and high-grade histologies according to the Working Party Formulation) were limited to treatment with one prior drug regimen. Patients with favorable histologies of NHL (low-grade histologies in the Working Party Formulation) had received prior treatment with single-agent alkalators and/or one drug combination. Thus, esorubicin was given as second-line treatment to patients with HD and unfavorable histologies of NHL, and as second- or third-line treatment to patients with favorable histologies of NHL. All patients had measurable disease and a life expectancy of at least 8 weeks. Peripheral blood counts were normal (leukocytes > 3,000 cells per microliter and platelets > 100,000 cells per microliter) unless there was evidence of bone marrow involvement by lymphoma. The serum creatinine was less than 2.0 mg/dL and the serum bilirubin was less than 2.0 mg/dL. Patients with a previous history of congestive heart failure or cardiac arrhythmia were ineligible. Patients were ineligible if the cumulative dose of prior doxorubicin exceeded 350 mg/m^2. Patients with a prior doxorubicin cumulative dose of less than 350 mg/m^2 were eligible for the protocol provided a radionuclide ejection fraction (EF) was greater than 50%. Patients were informed of the investigational nature of the study and written informed consent was obtained in accordance with institutional and Food and Drug Administration guidelines.

Treatment Plan

Based on a phase I study by Garewal et al,[18] patients received esorubicin, 30 mg/m^2 as a rapid intravenous (IV) infusion over 5 minutes through a side arm of a freely running IV infusion unless (1) the patients were older than the age of 65 years, (2) had received extensive previous pelvic or mediastinal irradiation, or (3) had bone marrow involvement with lymphoma resulting in low peripheral leukocytes or platelets. These patients received an initial dose of esorubicin of 25 mg/m^2. Esorubicin was administered every 21 days for a minimum of two cycles of therapy. Dose modifications were based on peripheral blood counts obtained on the day treatment was due. For patients having total leukocytes greater than 3,000 cells per microliter, granulocytes greater than 1,500 cells per microliter, and platelets greater than 100,000 cells per microliter, no changes in dose were made. For patients with total leukocytes of 2,000 to 3,000 cells per microliter, granulocytes of 1,000 to 1,500 cells per microliter, or platelets of 50,000 to 100,000 cells per microliter, esorubicin administration was delayed until there was peripheral blood count recovery, and the dose was reduced by 25%. For patients with total leukocytes less than 2,000 cells per microliter, absolute granulocytes less than 1,000 cells per microliter, or platelets less than 50,000 cells per microliter, esorubicin administration was delayed until there was peripheral blood count recovery, and the dose was reduced by 50%. Patients responding to esorubicin continued to receive the drug until there was evidence of disease progression or unacceptable toxicity. Cardiac toxicity was monitored with serial radionuclide EFs repeated at intervals of 150 mg/m^2 of esorubicin administered. The esorubicin was discontinued if there was a fall in the EF greater than 10%.

Definitions of Outcome

Response to treatment was classified as a complete remission (CR) if all clinical evidence of active disease resolved for a minimum of 4 weeks. A partial remission (PR) was defined as a 50% or greater decrease in the sum of the products of the maximum perpendicular diameters of all measured lesions lasting at least 4 weeks. Contingency χ^2 tests of statistical significance were used to compare remission rates. Exact 95% confidence intervals (CIs) for response rates were also calculated. Response duration was measured as relapse-free survival (RFS) from the date of CR or PR to the first sign of relapse, last follow-up, or death. Survival duration was measured from the date of registration to the date of death or last follow-up. All causes of death are included for survival and RFS estimates. Graphic representation of survival and RFS were performed using the method of Kaplan and Meier.[19] Statistical significance between patient groups was performed using the log-rank test of statistical significance.[20] All tests are two-sided.

RESULTS

Between August 1984 and March 1988, 97 patients from 33 institutions were registered onto the study. Nine patients were ineligible for the following reasons. Three patients had exceeded the eligibility criteria for prior treatment, having received too many drug regimens before registration; two patients began treatment with esorubicin before registration; one patient had a serum creatinine exceeding 2.0 mg/dL; and one patient had no baseline radionuclide EF. In addition, two patients were deemed ineligible after expert histologic review. Of the 88 eligible patients, 55 had received prior doxorubicin (62%) including all patients with unfavorable histologies of NHL. For patients who had received prior doxorubicin, the median cumulative dose was 217 mg/m^2 (range, 25 to 350 mg/m^2).

Some of the pretreatment patient characteristics and responses to treatment with esorubicin are summarized in Table 1. There were 59 men and 29 women with a median age of 61 years (range, 20 to 80 years). Overall, 33 of 88 patients (38%; 95% CI, 27% to 48%) responded to treatment. There were three CRs (3%) and 30 PRs (34%). All three CR patients previously received doxorubicin-containing combination chemotherapy and subsequently relapsed within 1 year of completing initial treatment. Overall response by histologic subtype included eight of 26 patients

Table 1. Patient Characteristics and Response to Treatment With Esorubicin

Characteristic	No. Patients	CR No.	CR %	PR No.	PR %
All patients	88	3	3	30	34
Histology					
Favorable NHL	26	1	4	7	27
Unfavorable NHL	43	2	5	12	28
Hodgkin's disease	19	0	0	11	58
Initial dose level					
30 mg/m^2	39	2	5	14	36
25 mg/m^2	49	1	2	16	33

with favorable NHL (31%; 95% CI, 14% to 52%), 14 of 43 patients with unfavorable NHL (33%; 95% CI, 19% to 49%), and 11 of 19 patients with HD (58%; 95% CI, 34% to 80%). Response did not vary by the initial dose of esorubicin administered, with responses seen in 16 of 39 patients (41%) receiving an initial dose of 30 mg/m^2 and in 17 of 49 patients (35%) receiving 25 mg/m^2 as the initial dose (P = .66). Prior treatment with doxorubicin did not correlate with response to esorubicin, with 32 of 55 nonresponding patients (58%) receiving prior doxorubicin compared with 22 of 33 responding patients (67%).

Twenty-six eligible patients are currently alive, and median follow-up for these patients is 26.0 months (range, 11.0 to 45.5 months). Overall survival did not differ significantly by histologic subtype (Fig 1, P = .10), but did vary by initial dose of esorubicin (P = .02). Those patients older than 65 years, those who had previously received extensive radiotherapy, and those who had low peripheral leukocytes or platelets due to bone marrow involvement and received 25 mg/m^2 esorubicin had a median survival of 8.9 months. The median survival was 27.3 months for patients who did not have these poor prognostic features, and who received an initial dose of 30 mg/m^2 esorubicin (comparison is not provided as the two patient groups are not comparable). RFS for 33 responding patients did not differ significantly by histologic subtype (Fig 2, P = .80) or initial dose of esorubicin (P = .24). The median time to relapse or death was 2.9 months for eight patients with favorable NHL, 24.9 months for 14 patients with unfavorable NHL, and 6.2 months for 11 patients with HD. Notably, there have been only three relapses in 12 responding patients followed from 1 to 4 years.

Toxicity of treatment with esorubicin is summarized in Table 2 for 87 assessable patients (one patient did not receive enough esorubicin to allow valid toxicity assessments). Table 2 tabulates the most severe toxicity during treatment with esorubicin, including a median of three treatment courses (range, one to 33) while administering a median of 60 mg/m^2 (range, 19 to 822 mg/m^2). Myelosuppression, especially neutropenia, was the most common and dose-limiting toxicity. Thirty-two of 39 patients (82%) treated with 30 mg/m^2 esorubicin and 33 of 48 patients (69%) treated with 25 mg/m^2 esorubicin developed leukopenia. The leukopenia was life-threatening (< 1,000 cells per microliter) in 13 of 39 patients (33%) treated at the higher initial dose and in seven of 48 patients (15%) treated at the lower initial dose. One patient died as a complication of treatment with esorubicin (30 mg/m^2 initial dose) secondary to sepsis associated with leukopenia. Three patients were shown to have a decrease in the radionuclide EF (≥ 10% change from baseline), but no patient developed symptoms or findings to suggest CHF. Phlebitis

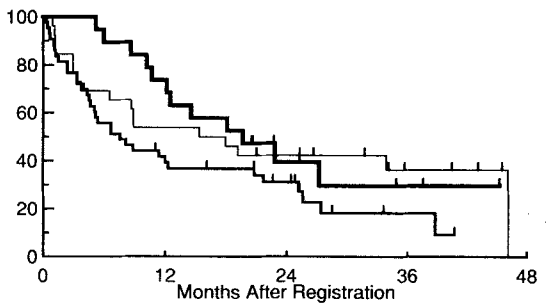

Fig 1. Overall survival by histologic subtype for 88 patients treated with esorubicin. (—) Favorable NHL, (—) unfavorable NHL, (—) HD.

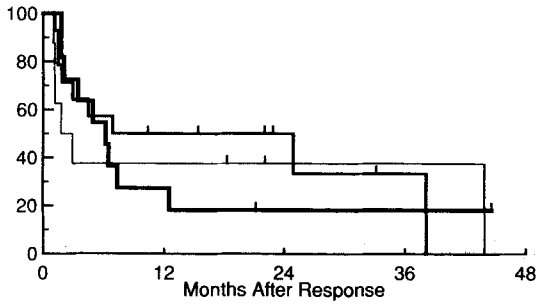

Fig 2. RFS by histologic subtype for 33 responding patients treated with esorubicin including 30 partial responders and 3 complete responders. (—) Favorable NHL, (—) unfavorable NHL, (—) HD.

Table 2. Toxicity of Treatment With Esorubicin for Patients Having Severe or Worse Complications Classified According to Initial Dose

Toxicity	Esorubicin Dose: 30 mg/m² (N = 39) No.	%	25 mg/m² (N = 48) No.	%
Alopecia (complete)	2	5		
Anemia (hemoglobin < 7 g/dL)	3	8	1	2
Cardiac (>10% decrease in EF)			3	6
Leukopenia				
1,000-2,000 cells/μL	7	18	18	37
<1,000 cells/μL	13	33	7	15
Vomiting (>6 times)	3	8	1	2
Thrombocytopenia				
25,000-50,000 cells/μL	2	5	2	4
<25,000 cells/μL	1	3	3	6
Phlebitis (severe)	1	3	2	4

was relatively common (17 of 87 patients, 20%) but gradually resolved without sequelae in most instances.

DISCUSSION

This phase II study indicates that esorubicin is an active single agent against NHL and HD as gauged by a 38% response rate in 88 assessable patients and a median RFS time of 6.2 months for all histologies combined. The duration of responses was remarkable for a proportion of patients as indicated by the relative flattening of the RFS curves at approximately 30% for patients with intermediate- and high-grade histologies of NHL, slightly higher for patients with low-grade histologies of NHL, and at approximately 15% for patients with HD. These findings are unusual for single-agent therapy of relapsing lymphoma and provide some justification for the use of single-agent experimental therapy (including drug analogs) at the time of first relapse in patients with malignant lymphomas. These results compare favorably with previous Southwest Oncology Group phase II trials of single-agent chemotherapy in relapsing lymphoma. For example, our previous trial of mitoxantrone resulted in a 24% response rate in 37 previously treated lymphoma patients with a median response duration of 7.7 months.[21] A phase II trial of bisantrene resulted in a 10% response rate in 40 patients, with a median response duration of only 4 months.[22] However, these previous studies included heavily pretreated patients, whereas the current study tested esorubicin at the time of first relapse.

The toxicity of treatment with esorubicin was generally acceptable with leukopenia being the dose-limiting toxicity in the majority of patients (Table 2). The dose chosen for initial treatment (25 mg/m² to 30 mg/m² depending on age and previous radiotherapy) appears to be an adequate dose of esorubicin, as 52% of patients at each dose level achieved significant myelosuppression (<2,000 leukocytes per microliter). The higher dose of esorubicin used in younger patients without prior radiotherapy (30 mg/m²) resulted in leukopenia below 1,000 cells per microliter in 44% of patients. This would appear to be the maximally tolerated dose-rate for esorubicin as used in an outpatient setting.

Because preclinical studies suggested that esorubicin might be less cardiotoxic, evidence of congestive heart failure was monitored closely. No patient developed overt symptoms or physical findings of congestive heart failure. Three patients (3%) who were all treated at the lower dose-rate of esorubicin were shown to have a decline in the EF based on serial radionuclide EFs of greater than 10% and less than 20%. This small frequency of a marginal decline in EF may not signal significant cardiotoxicity and may more accurately reflect the difficulty of reproducing radionuclide EF. Although we found no conclusive evidence of significant cardiac toxicity, our data may significantly underestimate the incidence of cardiac injury, as patients received a relatively low total dose of esorubicin (median cumulative dose, 217 mg/m² in patients receiving prior doxorubicin). The other toxicities as indicated in Table 2 were generally infrequent and reversible. Severe episodes of vomiting, thrombocytopenia, and phlebitis were infrequent. A relatively common, but mild or moderate side effect, was a syndrome of weakness and fatigue associated with esorubicin. The symptoms were reversible but could last up to 2 weeks following an injection with esorubicin.

The design of the current trial does not permit evaluation of esorubicin non-crossresistance with doxorubicin. All patients with intermediate- and high-grade NHL and all patients with HD had previously received doxorubicin as a component of combination chemotherapy as initial treatment. In these patients, the doxorubicin was not administered at maximally tolerated dose rates, and clinical resistance to doxorubicin cannot be determined. There was no significant difference in

response rates between patients with low-grade non-Hodgkin's lymphomas who had not received any previous doxorubicin and those patients with unfavorable histologies of NHL and patients with HD who had all received previous doxorubicin. However, Hill et al[23] have previously shown a complete absence of cross-resistance using esorubicin in a doxorubicin murine lymphoma cell line.[23] More recently, Coley et al[24] demonstrated esorubicin to be moderately effective against a doxorubicin-resistant human small-cell lung cancer cell line, but esorubicin was fully cross-resistant with doxorubicin in a murine mammary tumor cell line. Thus, there is conflicting in vitro data suggesting that esorubicin may be non-crossresistant with doxorubicin. A future clinical trial of esorubicin in patients carefully selected for doxorubicin-resistance is justified. Because such patients likely will not have received doxorubicin in maximally tolerated single or cumulative doses, other markers of doxorubicin resistance, such as p-glycoprotein expression, would be of particular interest.[25,26]

The results of the current trial suggest that esorubicin is an active single agent in patients with malignant lymphoma at the time of first relapse based on a 38% response rate and prolonged remissions in 36% of responsive patients. Analysis of the toxicity of treatment with esorubicin suggests that 30 mg/m^2 is an appropriate dose-rate for treatment in an outpatient setting using a 21-day schedule and is in accord with the findings of the phase I study.[18] The activity of esorubicin in previously treated patients, together with preclinical studies suggesting possible non–cross-resistance with doxorubicin, suggests that esorubicin should be pursued as a possibly effective treatment option in patients with clinical evidence of drug resistance.

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