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Epirubicin: A phase II study in recurrent small-cell lung cancer

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Summary. Epirubicin (4′-epidoxorubicin), an analogue of doxorubicin (Adriamycin), has established activity in the treatment of small-cell lung cancer (SCLC) when used at doses of 75 to 120 mg/m^2 in previously untreated patients. We completed a phase II study of epirubicin (85 mg/m^2 given intravenously at 3-week intervals) in 20 patients with recurrent SCLC, all of whom had received prior combination chemotherapy. Of 19 patients who were assessable for response, 2 achieved a complete response and 2 a partial response, for an overall response rate of 4/19 (21%); 95% confidence interval, 8%–43%). Myelosuppression and alopecia were the most frequent toxicities; epirubicin was otherwise well tolerated, with other toxicities such as nausea and vomiting being infrequent or mild. Epirubicin at a dose of 85 mg/m^2 exhibits modest single-agent activity in previously treated SCLC and is generally well tolerated. Given as a single agent or in combination with other well-tolerated drugs, epirubicin would be suitable in cases in which palliation of symptoms without undue toxicity is required in the management of previously treated SCLC.

Introduction

Epirubicin (4′-epidoxorubicin) is a new analogue of doxorubicin (Adriamycin) that has been shown to be an active single agent in previously untreated extensive-stage small-cell lung cancer (SCLC) when given at doses of 75–120 mg/m^2 [3, 5, 9]. Milligram for milligram, epirubicin is reported to cause less cardiotoxicity (14) and less nausea and vomiting than doxorubicin [4, 6, 13]. However, on a milligram-for-milligram basis, the doses of the two drugs that induce equivalent myelosuppression are not necessarily identical [4, 8]. In view of the favourable toxicity profile of epirubicin, most centres investigating the drug have proceeded to high-dose treatment at doses of 100–120 mg/m^2 [3, 9]. However, in cases in which the objective of therapy is palliation, lower-dose therapy may be preferable and deserves exploration in salvage regimens.

Although combination chemotherapy achieves high response rates with associated survival benefit in SCLC, nearly all patients relapse within 12 months [1, 2, 12]. Since first-line therapy frequently employs agents such as carboplatin and etoposide [1, 2], regimens including an anthracycline such as doxorubicin or epirubicin are often selected for salvage therapy. We report herein our experience with epirubicin given at an intravenous dose of 85 mg/m^2 at 3-week intervals in the treatment of 20 patients with recurrent SCLC.

Patients and methods

Between March 1988 and May 1989, 20 patients with histopathologically proven, evaluable or measurable recurrent SCLC were entered in the present study after they had given their written informed consent. In all, 12 were men, and the median age was 64 years (range, 44–78 years). All had undergone prior combination chemotherapy, although none had previously received doxorubicin. Eligibility criteria included a normal full blood count, the absence of cardiac symptoms, a left ventricular ejection fraction (LVEF) of $\geq 50\%$ as measured by gated heart-blood pool scan, and the absence of significant renal or hepatic dysfunction as defined by serum creatinine and liver-function tests within 1.5 times the upper limit of normal. Patients with central nervous system metastases and those with an Eastern Cooperative Oncology Group performance status (ECOG PS) [11] of 4 were excluded.

Epirubicin was given at a dose of 85 mg/m^2 at 3-week intervals by intravenous injection over 10 min into the side-arm of a fast-flowing normal saline infusion. Patients received a minimum of two and a maximum of six cycles of epirubicin unless there was evidence of either disease progression after only one cycle or severe toxicity. Intravenous metaclopramide (20 mg) and dexamethasone (10 mg) and oral lorazepam (2 mg) were given routinely to minimise any associated nausea or vomiting. Full blood counts, determinations of plasma urea, electrolytes and serum creatinine, and liver-function tests were performed weekly. A physical examination, chest X-ray and toxicity notation were performed at study entry and at the commencement of each cycle.

Standard criteria for response and toxicity were used [15]. Patients were considered to be evaluable for response if they had completed two

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Table 1. Response related to the site of disease in 19 patients

Disease site	Patients (*n*)	Responses
Mediastinum	9	1 (11%)
Lung	2	0 –
Lymph nodes	4	0 –
Abdomen	2	1 (50%)
Liver	2	2 (100%)

Table 2. Toxicity of epirubicin: worst toxicity recorded in 20 patients

	Number of patients (%) with toxicity of WHO grade				
	0	I	II	III	IV
WBC[a]	10 (50)	3 (15)	3 (15)	2 (10)	2 (10)
Platelets	16 (80)	0	0	2 (10)	2 (10)
Nausea/vomiting	13 (65)	4 (20)	3 (15)	0	0
Alopecia	9 (45)	2 (10)	2 (10)	7 (35)	0
Mucositis	17 (85)	0	3 (15)	0	0
Diarrhoea	19 (95)	1 (5)	0	0	0

[a] Nadir WBC count

cycles of treatment; however, those whose disease progressed after the completion of only one cycle were included and classed as treatment failures. All patients were assessed for toxicity, whether or not they had completed two cycles of treatment.

Results

Of the 20 patients enrolled in the study, 1 was not assessable for response because treatment was abandoned after the first cycle due to toxicity. Of the 19 assessable subjects, 2 achieved a complete response and 2 a partial response, for an overall response rate of 4/19 (21%; 95% confidence interval, 8%–43%). Two patients exhibited stable disease and six progressive disease after two cycles of therapy. Seven subjects showed evidence of progressive disease after just one cycle. The response according to the site of disease is shown in Table 1. The time to response was two cycles (6 weeks) in both partial responders and two and eight cycles, respectively, for the complete responders.

Ten patients had achieved a complete remission and four had attained a partial remission during prior treatment, but all relapsed subsequently. Six had failed first-line treatment. The median time to relapse following the completion of first-line treatment was 18 weeks (range, 4–92 weeks). In all, 3 of the 14 patients who had responded to and 1 of the 6 who had failed first-line therapy subsequently responded to epirubicin. The median time from the cessation of first-line therapy until the commencement of epirubicin was 35 weeks (range, 11–92 weeks) for the responders and 14 weeks (range, 4–70 weeks) for the non-responders.

All responders to epirubicin have now relapsed. The duration of response for the two complete responders was 4 and 5 months respectively, and that for the 2 partial responders was 2 and 6 months, respectively. The two patients with stable disease exhibited progression after 2 and 6 months, respectively. The median survival of all patients from the time of diagnosis was 10 months (range, 3–29 months) and that from the time of commencement of epirubicin was 9 weeks (range, 1–47 weeks).

Toxicities encountered during the study are shown in Table 2. The major toxicity was myelosuppression, with leucopenia of grade I occurring in 3 cases (15%); that of grade II, in 3 (15%); that of grade III, in 2 (10%); and that of grade IV, in 2 (10%) patients. The median WBC nadir was $3.2 \times 1{,}000/mm^3$ (range, $0.1–15.7 \times 1{,}000/mm^3$). Three patients developed febrile neutropenia, all of whom were successfully treated with intravenous antibiotics (gentamycin and piperacillin). Two of these subjects, including one who had achieved a partial remission, refused further therapy. Grade III thrombocytopenia was noted in 2 patients (10%) and grade IV thrombocytopenia developed in a further 2 cases (10%); however, those with grade IV thrombocytopenia had shown low platelet counts at study entry (67,000 and $74{,}000 \times 10^9/l$). The median platelet nadir was $212{,}000 \times 10^9/l$ (range, 12,000–$471{,}000 \times 10^9/l$).

Other toxicities observed included grade II or III alopecia in a total of 9 patients (45%) and mucositis in 3 cases (15%). In all, 4 subjects (20%) complained of nausea only, and 3 (15%) experienced transient vomiting; none required additional antiemetic therapy over and above that given routinely. No clinical evidence of cardiac toxicity was noted; however, gated heart-pool scans were not repeated during treatment. There were no treatment-related deaths.

Discussion

Despite the high response rates achieved using combination chemotherapy in SCLC, most patients eventually relapse. Although single-agent response rates for drugs active in SCLC, including doxorubicin, amount to $\geq 30\%$ in untreated patients [7], most have meagre activity in previously treated patients, and the median survival of relapsed individuals is disappointing, usually being of the order of only about 2 months [10]. For salvage treatment, drugs that have not previously been used and that may be potentially non-cross-resistant are usually selected.

In this setting, further chemotherapy should be considered for palliative rather than curative intent. Relief of symtoms such as pain, shortness of breath or hemoptysis should be the major objective of treatment. As prolonged survival is rarely attained, the toxicity of salvage therapy should not impair the quality of the time remaining for this group of patients. In these respects, epirubicin proved to have modest activity but, notably, was not associated with severe toxicity in most cases in this series.

To our knowledge, there are no studies comparing the activity or toxicity of epirubicin with those of doxorubicin in the treatment of SCLC. Studies in other solid tumours suggest that the activities of these two drugs are similar but that the incidence of nausea, vomiting, mucositis, cardiotoxicity and, possibly, myelo-suppression may be lower in patients receiving epirubicin [4, 6, 8, 13, 14]. However, a direct comparison of toxicities is hampered by the lack of established dose equivalents for the two agents. Moreover,

we have been unable to find reports of the use of single-agent doxorubicin as salvage therapy for SCLC.

In conclusion, epirubicin given intravenously at a dose of 85 mg/m^2 at 3-week intervals demonstrated modest single-agent activity in previously treated patients with SCLC and was generally well tolerated. Given as a single agent or in combination with other well-tolerated drugs, epirubicin would appear to be suitable in cases in which palliation of symptoms without undue toxicity is required in the management of previously treated patients with SCLC.

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