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*Short communication*

# Experience with intermediate-dose (110–120 mg/m$^2$) epirubicin

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**Summary.** A total of 23 patients with advanced malignancies received escalating doses of epirubicin (100–120 mg/m$^2$) i.v. at 3-week intervals; 15 had received previous chemotherapy. In all, 46 courses of chemotherapy were given. Mucositis (grade II or III) occurred in 47% of courses at 120 mg/m$^2$, but in only 15% of courses at 115 mg/m$^2$. Myelotoxicity was manifest as leucopenia, with a median white blood count nadir of 1.9 (range, 0.8–7.0) × $10^9$/l. Nausea and vomiting were generally well controlled by prophylactic antiemetic therapy. Alopecia was WHO grade 0 in 2 patients, grade I in 1, grade II in 5 and grade III in 14. No renal or hepatic toxicity was noted, and there were no episodes of congestive cardiac failure. One fatal coronary thrombosis (proven at post-mortem examination) occurred 48 h after a dose of 115 mg/m$^2$. Four patients developed thrombophlebitis at the injection site that was not dose-related; it occurred at doses between 100 and 120 mg/m$^2$. Two patients who had been given chemotherapy in the past had complete responses (one penile carcinoma, one gastric carcinoma). Six patients had partial responses, including two with breast cancer, one with gastric cancer and three with sarcoma. Intermediate-dose epirubicin was well tolerated up to 120 mg/m$^2$, when mucositis became a significant clinical problem. Preliminary data suggest promising activity in gastric cancer, breast cancer and a variety of sarcomas.

## Introduction

Epirubicin is an analogue of doxorubicin that was developed primarily to avoid the cumulative cardiotoxic effects of doxorubicin known to occur at doses > 550 mg/m$^2$. The antitumour effect of both drugs is similar [4], but endomyocardial biopsy and echocardiographic studies [4–7] have shown that a significantly higher cumulative dose of epirubicin may be given before cardiomyopathy is encountered. Myelosuppression and mucositis are the main acute, dose-limiting toxicities of doxorubicin; however, the acute dose-limiting toxicity for epirubicin is unclear. Reversible myelosuppression has been reported in earlier studies of epirubicin up to 105 mg/m$^2$ [3]. In addition, and unlike doxorubicin, stomatitis has been reported in only 5% of patients at a dose of 90 mg/m$^2$ [1]. In a recent report [1], only 2 of 12 patients with refractory lymphoma given epirubicin at doses of 120–150 mg/m$^2$ developed severe mucositis, which occurred irrespective of the dose given. The main aim of this study was to determine the dose of epirubicin that could safely be given in the outpatient setting with the minimum of toxicity. A starting dose of 100 mg/m$^2$ was selected because epirubicin is known to be well tolerated below this dose.

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## Patients and methods

Entry criteria for the trial were as follows: a performance status of 2 or better on the ECOG scale, a life expectancy of > 2 months, no radiotherapy or chemotherapy for at least 4 weeks prior to the study (6 weeks for nitrosoureas and mitomycin-C), a white blood counts (WBC) of > 4 × $10^9$/l, platelets of > 100 × $10^9$/l, serum bilirubin of < 20 μmol/l, and serum creatinine of < 150 μmol/l. Patients who were poor medical risks were excluded. Informed consent was obtained from all patients. Patients were evaluated prior to treatment and every 3 weeks and seen weekly to assess toxicity and repeat the full blood count.

Epirubicin (Pharmorubicin; Farmitalia Carlo Erba) was provided as a sterile, pyrogen-free, red, freeze-dried powder in vials of 10 and 50 mg epirubicin hydrochloride with lactose. for reconstruction the 10-mg vial was dissolved in 5 ml water; it was injected i.v. over 3–5 min in a freely running i.v. infusion of saline.

The dose escalation was planned as follows: 100, 110, 115 and 120 mg/m$^2$. In the absence of toxicity, the next scheduled dose was given on each successive course. A scheduled course was delayed by 1 week if haematological recovery was incomplete. Doses were adjusted for each course according to the lowest value of WBC and platelets, measured weekly during the previous course. Treatment was continued for at least two courses unless clearly not in the patients' interest. Response to treatment and toxicity were assessed using WHO criteria [6].

## Results

A total of 23 patients (13 men, 10 women) with a mean age of 61.4 years (range, 25–87 years) received 45 courses of epirubicin; 15 (65%) had received previous chemotherapy.

**Table 1.** Dose of epirubicin

| Dose ($mg/m^2$) | Number of courses | Number of patients |
|---|---|---|
| 100 | 6 | 4 |
| 110 | 10 | 10 |
| 115 | 14 | 12 |
| 120 | 15 | 12 |

Table 1 shows courses according to the dose of epirubicin. Only 16 courses were given at 100 and 110 $mg/m^2$ because of the lack of toxicity at these dose levels.

*Response to epirubicin*

In all, 21 patients were evaluable for response (Table 2). Two patients who had received previous chemotherapy had complete responses; one patient with metastatic squamous carcinoma of the penis who had previously received methotrexate, cisplatin and etoposide had a complete response of 3 months duration, and one patient with gastric cancer previously treated with FEM (5-fluorouracil, epirubicin and mitomycin-C) had a complete response of 5 months' duration. Six patients, one of whom had received previous chemotherapy, had partial responses. Six patients who had received previous chemotherapy had stable disease; of seven patients who had progressive disease, four had previously undergone chemotherapy.

*Toxicity*

All patients were evaluable for toxicity. Table 3 summarises the myelotoxicity. Analysis of the effect of previous chemotherapy on the extent of myelosuppression is shown in Tables 4 and 5. Over 46 courses, nausea and vomiting was WHO grade 0 in 29, grade I in 5, grade II in 6, grade III in 1 and grade IV in 1. Alopecia was WHO grade 0 in 2, grade I in 1, grade II in 5 and grade III in 14. Mucositis became a significant problem at 120 $mg/m^2$, at which level 50% of patients developed grade II or III toxicity (Table 6). Mucosal toxicity was generally observed on day 7 after epirubicin, resolving by day 14. No renal or hepatic toxicity was encountered. Grade II thrombophlebitis occurred in one patient at 100 $mg/m^2$, one at 110 $mg/m^2$, one at 115 $mg/m^2$ and one at 120 $mg/m^2$. No patient developed congestive cardiac failure. One patient had a fatal inferior myocardial infarction 48 h after a dose of 115 $mg/m^2$; she had previously been treated with combinations of methotrexate, melephalan and mitomycin-C as well as cyclo-

**Table 2.** Sites of primary tumour and response to epirubicin

| Site of primary tumour | Number of patients | Stable disease | Not evaluable | Progressive disease | Partial response | Complete response |
|---|---|---|---|---|---|---|
| Breast | 9 | 4 | 1 | 2 | 2 | |
| Gastric | 4 | | 1 | 1 | 1 | 1 |
| Colorectal | 1 | | | 1 | | |
| Melanoma | 2 | | | 2 | | |
| Ewing's sarcoma | 1 | | | | 1 | |
| Rhabdomyosarcoma | 1 | | | | 1 | |
| Mesothelioma | 1 | 1 | | | | |
| Histiocytoma | 2 | | | 1 | 1 | |
| Penis | 1 | | | | | 1 |
| Small-cell bronchial | 1 | 1 | | | | |
| Totals | 23 | 6 | 2 | 7 | 6 | 2 |

**Table 3.** White blood count and platelet nadirs following epirubicin (45 courses)

| Dose | WBC ($\times 10^9/l$) | | | | | |
|---|---|---|---|---|---|---|
| | | | Nadir day | | Recovery day | |
| | Median | Range | Mean | Range | Mean | Range |
| 100 $mg/m^2$ | 4.85 | 0.8–72 | 17 | 7–35 | 25 | 21–42 |
| 110 $mg/m^2$ | 5.2 | 1.3–23.2 | 11 | 7–14 | 21 | 21 |
| 115 $mg/m^2$ | 3.6 | 0.9–10.4 | 13 | 7–21 | 21 | 21 |
| 120 $mg/m^2$ | 4.2 | 0.6–20.3 | 18 | 7–49 | 27 | 21–56 |
| Dose | Platelet ($\times 10^9/l$) | | | | | |
| | | | Nadir day | | Recovery day | |
| | Median | Range | Mean | Range | Mean | Range |
| 100 $mg/m^2$ | 325 | 76–563 | 14 | 14 | 21 | 21 |
| 110 $mg/m^2$ | 440 | 121–959 | 0 | 0 | 0 | 0 |
| 115 $mg/m^2$ | 308.55 | 88–837 | 7 | 7 | 0 | 0 |
| 120 $mg/m^2$ | 290 | 53–816 | 7 | 7 | 0 | 0 |

**Table 4.** Haematological toxicity of epirubicin by dose according to previous chemotherapy (45 courses)

| Toxicity (WHO) | WBC nadir, no previous treatment (mg/m²) | | | | WBC nadir, chemotherapy ≤3 drugs (mg/m²) | | | | WBC nadir, chemotherapy >3 drugs (mg/m²) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 100 | 110 | 115 | 120 | 100 | 110 | 115 | 120 | 100 | 110 | 115 | 120 |
| 0 | 1 | 2 | 1 | 1 | | 2 | | 1 | | | | 1 |
| I | | 1 | 1 | | | | 1 | | | | | |
| II | | 1 | 2 | | 2 | | 2 | 1 | | | | |
| III | | | 2 | 1 | | 2 | 1 | 3 | | 1 | 1 | 1 |
| IV | | | | | | | | 2 | 1 | | 1 | |
| Toxicity (WHO) | Platelets, no previous treatment (mg/m²) | | | | Platelets, chemotherapy ≤3 drugs (mg/m²) | | | | Platelets, chemotherapy >3 drugs (mg/m²) | | | |
| | 100 | 110 | 115 | 120 | 100 | 110 | 115 | 120 | 100 | 110 | 115 | 120 |
| 0 | 1 | 4 | 4 | 3 | 2 | 4 | 4 | 6 | | 1 | 2 | 2 |
| I | | | 1 | | | | | | 1 | | | |
| II | | | | | | | | 1 | | | | |
| III | | | | | | | | | | | | |
| IV | | | | | | | | | | | | |

**Table 5.** Haematological toxicity of epirubicin according to previous chemotherapy (45 courses)

| Toxicity (WHO) | No previous treatment | | Chemotherapy ≤3 drugs | | Chemotherapy >3 drugs | |
|---|---|---|---|---|---|---|
| | WBC | Platelets | WBC | Platelets | WBC | Platelets |
| 0 | 8 | 17 | 5 | 20 | 1 | 5 |
| I | 2 | 1 | 1 | 0 | 0 | 1 |
| II | 4 | 0 | 7 | 1 | 0 | 0 |
| III | 4 | 0 | 5 | 0 | 3 | 0 |
| IV | 0 | 0 | 3 | 0 | 2 | 0 |

**Table 6.** Mucosal toxicity according to previous chemotherapy (45 courses)

| Toxicity (WHO) | No previous treatment (dose, mg/m²) | | | | Previous treatment (dose, mg/m²) | | | |
|---|---|---|---|---|---|---|---|---|
| | 100 | 110 | 115 | 120 | 100 | 110 | 115 | 120 |
| 0 | 2 | 4 | 5 | 1 | 2 | 2 | 4 | 5 |
| I | | 1 | 2 | 0 | 1 | 3 | 1 | 2 |
| II | | | 1 | 1 | 1[a] | | | 4 |
| III | | | 0 | 1 | | | 1 | 1 |
| IV | | | 0 | | | | | |

[a] This patient was leucopenic at the time of mucositis, which therefore might not have been drug-related

phosphamide, vincristine and epirubicin (cumulative dose, 110 mg). Post-mortem examination revealed a fresh thrombus in the left anterior descending coronary artery. Apart from this case, serial ECGs in all other patients were normal.

## Discussion

Mucositis was the dose-limiting toxicity for epirubicin, occurring at 120 mg/m². This contrasts with earlier phase I studies [4] where myelosuppression was dose-limiting at 90 mg/m². In our experience, 50% of courses at a dose of 120 mg/m² were associated with significant mucositis. Case et al. [2] reported a lower incidence of mucositis; however, it is interesting that in the present study mucositis usually occurred between days 7 and 14 after treatment and therefore might easily have been missed if patients had not been reviewed weekly.

Myelosuppression was not a major side effect. Predictably, previously treated patients were most sensitive, particularly those who had received more than three different cytotoxic drugs. The white blood cells were predominantly affected, and no patient developed a platelet count of $< 50 \times 10^9$/l. There were no septicaemic fatalities. Thrombophlebitis was a problem in four patients, three of whom received additional courses of epirubicin without further occurrence. Apart from the patient who developed a coronary thrombosis, there was no evidence of cardiotoxicity. Nausea and vomiting were not significant, and the clinical

impression was that epirubicin was better tolerated in this regard than doxorubicin.

Epirubicin had useful antitumour activity, producing partial or complete responses in 8 of the 22 patients; 2 of these had received previous chemotherapy that included doxorubicin and epirubicin at conventional doses. Thus, intermediate-dose epirubicin may produce a response in patients who have relapsed or progressed after treatment with lower-dose epirubicin.

In conclusion, the major toxicity of epirubicin is mucositis, which occurs at 120 mg/m$^2$; below this dose it is extremely well tolerated. Its relative lack of toxicity compared with doxorubicin suggests that epirubicin may have significant clinical advantages.

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