Eur J Cancer Clin Oncol, Vol. 24, No. 8, pp. 1379–1380, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

Clinical Trials Summaries

Esorubicin in Advanced Ovarian Epithelial Cancer

A Phase II Study of the EORTC Gynecological Cancer Cooperative Group

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INTRODUCTION

ESORUBICIN (4′-deoxydoxorubicin) is a derivative of doxorubicin and has shown significant activity against a variety of experimental tumor systems [1]. In animal models it was shown to be appreciably less cardiotoxic than doxorubicin [2]. Phase I studies showed myelosuppression to be dose-limiting. Administration of 30 mg/m^2 intravenously in a 3-weekly schedule was proposed for phase II trials [3].

This is a report of a phase II study in ovarian cancer patients who failed standard chemotherapy regimens. The purpose was to determine the response rate in this group of patients and to further characterize the toxic effects of esorubicin.

MATERIALS AND METHODS

Patients with progressive FIGO stage III–IV, measurable ovarian cancer were entered in the study. Patient eligibility criteria included: age <75 years, WHO performance status ≤2, no prior chemotherapy with anthracyclines, nitrosoureas or mitomycin C. Hormone therapy and chemotherapy had to be stopped for at least 4 weeks prior to initiation of esorubicin administration and all relevant toxic manifestations resolved. Patients were not allowed to have a second tumor apart from cone-biopsied *in situ* carcinoma of the uterine cervix and adequately treated basal cell carcinoma of the skin, or to have signs or symptoms of brain metastases. Patients should have measurable and/or evaluable disease, outside previously irradiated areas and white blood cells (wbc) count >4 × 10^9/l, platelet count >100 × 10^9/l and adequate cardiac, kidney and hepatic functions.

Pretreatment studies included history and physical examination, complete blood counts, a 12-channel biochemical screen, chest film and abdominal CT scan and/or echoscopy. Treatment consisted of esorubicin 30 mg/m^2 intravenously as a rapid injection once every 3 weeks.

Dosage adjustments at time of retreatment were made taking into account both the lowest values of wbc and platelets, based on weekly measurements, and the values at time of retreatment. Patients were evaluable for toxicity if they had completed one treatment cycle and for response after two cycles. Toxicities and responses were defined according to the WHO response criteria for measurable and evaluable disease [4]. Early death

Accepted 21 March 1988.
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due to progressive disease was evaluable as treatment failure, i.e. progression.

RESULTS

Twenty-three patients were entered by eight institutions.

Two of the patients entered proved to be ineligible: one because of no measurable lesions and the other because of a poor performance status.

Of the 21 eligible patients one died within 24 h after the first esorubicin dose of an acute cardiac event (heart failure, ECG compatible with myocardial infarction).

The characteristics of the 20 fully evaluable patients were as follows: median age 58 years (range 44–73), performance status 0: 5, 1: 13 and 2: 2. All patients had prior surgery, all but one had prior chemotherapy and only one had prior adjuvant radiotherapy but measurable lesions outside the irradiated area. A median number of five treatment cycles (range 2–10) were given. One patient showed a partial response lasting 5 months. In 10 patients the disease remained stable for 4–19 months and nine progressions were reported.

Esorubicin was generally well tolerated. The non-hematological side-effects were as follows: nausea and vomiting occurred in 15 patients (75%) and was grade 3 in three patients (15%). Diarrhea was reported in 10% of the patients (1 grade 3). Previous treatment and its related hair loss prevented an exact estimation of the degree of hair loss in our patient population. A local skin reaction at the infusion site was observed in two patients.

Progressive angina pectoris and subendocardial infarction (+ pulmonary edema) was observed in a patient who was stable on nitrates prior to treatment with esorubicin, accounting for two observed cardiac events in the 21 eligible patients.

The hematological toxicity observed was generally mild. The median wbc nadir was $1.5 \times 10^9/l$ (range 0.5–2.9) and the median platelet nadir was $107 \times 10^9/l$ (range 24–198). They both occurred on day 14. Dose modification did not occur, dose escalation was performed in one patient.

DISCUSSION

In view of the toxicities reported here and its minimal antitumor activity further investigations of a possible role for esorubicin to replace doxorubicin in treatment regimens for advanced ovarian cancer do not seem warranted.

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