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Short communication

A phase II study of oral idarubicin in advanced recurrent or refractory ovarian carcinoma

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Summary. Oral idarubicin (40 mg/m^2 in 3–4 divided doses over 24 h every 21 days) was tested in a group of patients with drug-resistant ovarian carcinoma. None of 13 patients responded and the study was discontinued. Toxicity was acceptable, with neutropaenia being dose-limiting. It seems unlikely that idarubicin has significant activity in this disease although phase II studies should ideally be conducted in less heavily pretreated patients.

Introduction

Despite much-improved response rates following the introduction of cisplatin-based combination chemotherapy for the treatment of advanced ovarian carcinoma, most patients relapse, and 5-year survival rates are below 20% even in the most optimistic series [7]. Response rates to second-line regimes are very variable (20%–60%), depending on primary responsiveness and time to relapse, but median survival has been <9 months in all trials. There is therefore a real need for new, more active cytotoxic agents in this disease.

Idarubicin (4-demethoxydaunorubicin – NSC 256,439) is an oral anthracycline analogue synthesized by Farmitalia Carlo Erba [1]. Phase II studies have shown that the drug possesses activity in solid tumours such as breast cancer [6] as well as leukaemia [4]; this study was designed to assess whether the drug is active in recurrent epithelial ovarian cancer.

Patients and methods

All patients had histologically proven ovarian carcinoma that was considered to be incurable and had received at least one combination of chemotherapy that contained cisplatin. The median time from diagnosis to trial entry was 11 months (range, 6–34 months). All had measurable or evaluable disease and were expected to live at least 3 months. None had undergone prior anthracycline therapy or had received radiotherapy in the preceding 4 weeks, and all had a performance status of at least 2 on the WHO scale. Patients with organ dysfunction, CNS involvement and other medical conditions that contra-indicated chemotherapy were excluded.

This was an open, uncontrolled study using a two-stage accrual plan based on the rules defined by Gehan. Idarubicin was given orally at a dose of 40 mg/m^2 in 3–4 divided doses over 12 h. Dosing was repeated at 21-day intervals if the peripheral counts were adequate. Doses were modified for neutropaenia, thrombocytopaenia and hyperbilirubinaemia. If the patient tolerated treatment without toxicity, there was a provision for increasing the dose by increments of 5% per course. Routine antiemetic therapy was carried out (domperidone, 20 mg p. o. t. d. s.) in all patients.

Pretreatment assessment included a physical examination, full blood count and biochemical screen, chest X-ray, an ultrasound examination of the abdomen/pelvis and an ECG. Assessment of response was carried out every 3 weeks. Response and toxicity criteria were those defined by the WHO.

Any patient with progressive disease represented a treatment failure and was withdrawn from the study. Patients with stable disease after three cycles of idarubicin were eligible to continue at the discretion of their physician. Those slowing an objective response after three cycles continued to six treatments, with further idarubicin being given at the discretion of the treating physician.

Results

A total of 13 patients entered the study; the mean age was 53.2 years (range, 36–74 years). In all, 1 patient had previously received whole abdomino-pelvic radiotherapy; 11, chlorambucil; 3, cyclophosphamide; 12, cisplatin; and 3, carboplatin. Prior partial response, of short duration, to first-line therapy was seen in three patients; the remainder were unresponsive to primary alkylating chemotherapy and second-line cisplatin-based chemotherapy, apart from one who actieved a complete response on second-line cisplatin.

All patients had progressive disease on idarubicin and therapy was discontinued. Progression and clinical deterioration was noted after one cycle only in six patients, two cycles in six cases and three cycles in one patient. All patients entering the study subsequently died, with a median survival of 4.0 months (range, 25 days to 9 months) from trial entry.

The median white cell count at day 21 was 2.45×10^9/l (range, $1.0–3.0 \times 10^9$/l). Of ten patients proceeding to a second cycle of idarubicin, only one had no delay due to neutropaenia; the median duration of delay was 10.5 days (range, 7–14 days). There was no significant anaemia, although thrombocytopaenia (87×10^9cells/l) after two

cycles of idarubicin was seen in one patient. Non-haematological toxicities included nausea and vomiting (grade 3 in eight patients), diarrhoea (grade 2 in two patients), lethargy (1), tingling in hands and feet (1), shivering and fever (1), malaise (1) and skin rash (1).

Discussion

This phase II trial of idarubicin in a group of heavily pretreated patients with refractory or recurrent ovarian carcinoma failed to show that the drug had any useful activity. Although doxorubicin has often been included in standard combinations for advanced ovarian carcinoma, there are data showing that it is ineffective when used as a second-line drug [5]; furthermore, a recent randomised trial has shown that this drug does not improve survival when added to cisplatin with or without cyclosphosphamide [3]. With this background, it is perhaps not surprising that idarubicin showed no activity in this study. Additional data suggesting that responses in these patients were unlikely come from the report by Blackledge et al. [2], which showed that in a series of phase II studies in ovarian carcinoma, responses were rarely, if ever, seen in patients who had received two or more chemotherapy regimens. Because of the extremely poor results – progression after one or two cycles in all but one patient – the study was discontinued after 13 patients had been accrued.

The present data suggest that idarubicin is unlikely to be useful in ovarian carcinoma. Ideally, however, the drug needs to be tested in patients who have relapsed after responding to initial chemotherapy.

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