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Lack of Activity of Cyclophosphamide in Ovarian Cancer Patients Refractory to *cis*-Dichlorodiammine Platinum

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Summary. *Twenty-three ovarian cancer patients refractory to first-line chemotherapy consisting of cis-dichlorodiamminoplatinum used as a single agent (50 mg/m² IV every 4 weeks) were admitted to this study. They received cyclophosphamide as an IV push at a dose of 1 g/m² every 3 weeks. They were evaluable for response after at least two cycles. None of the 18 evaluable patients responded: 15 (83%) showed rapid progression and three (17%) no change. Except in one case of severe leukopenia hematological toxicity was acceptable. Some (30%) of the patients experienced intractable vomiting on the day of cyclophosphamide administration.*

Introduction

It has been reported that *cis*-dichlorodiammine platinum (DDP) may be effective in about one-third of advanced ovarian cancer patients resistant to cyclophosphamide (CTX) [1, 2]. Whether CTX is equally effective in patients resistant to DDP is an open question.

We therefore considered it worthwhile to evaluate the efficacy of CTX given intermittently at relatively high doses in patients resistant to DDP as a single agent.

Patients and Methods

Twenty-three patients, ranging in age from 42 to 76 years and with advanced ovarian cancer refractory to *cis*-platinum therapy, entered this study. Criteria for eligibility included objectively evaluable and progressive disease, life expectancy at least 6 weeks, performance status ≥ 70 on the Karnofsky scale, an interval of at least 4 weeks since previous treatment, WBC ≥ 4,000/μl, platelets ≥ 150,000/μl, and normal hepatic and renal functions. Of the 23 patients, 18 were in stage III and five in stage IV as judged by pleural effusion, and lung or liver metastases; five patients had ascitic effusions. In 55% of patients the diameter of the largest residual tumor after primary surgery was > 10 cm. The median interval from initial diagnosis was 4 months (range 2–9). None of these patients had responded to previous treatment with *cis*-platinum alone, 50 mg/m² every 4 weeks, administered until disease progression for a median of four treatment cycles (range 2–7).

Cyclophosphamide (CTX) was administered as in IV push at a dose of 1 g/m². Therapy was repeated every 3 weeks if the WBC count was ≥ 4,000/μl and the platelet count ≥ 150,000/μl on the day of drug administration. If the WBC was < 4,000/μl and/or the platelet count < 150,000/μl, therapy was delayed for 1 week. After this time, if WBC was ≥ 4,000/μl and platelet count ≥ 150,000/μl, treatment was resumed at the full dosage; if WBC was 3,000–4,000/μl and/or platelet count 100,000–150,000/μl treatment was resumed at two-thirds of the full dose (650 mg/m²); if WBC was < 3,000 and/or platelet count < 100,000/μl, treatment was delayed until blood cell counts recovered and were above these thresholds, and was then resumed at two-thirds of the full dose for all subsequent cycles.

Patients were evaluable for toxicity after one cycle of therapy, regardless of subsequent treatment. They were evaluable for response after at least two cycles of therapy. Partial response (PR) was defined as a reduction in the sum of the tumor diameters by > 50% for at least 1 month, with no ascitic effusion persisting. No change (NC) was defined as a < 50% reduction or a < 25% increase in the sum of tumor diameters for at least 1 month; if ascitic effusion was present these changes were to be associated with a lower fluid production rate, documented by a longer interval between paracenteses. Progressive disease (NR) was defined as a > 25% increase in the sum of tumor diameters, the appearance of new lesions, or a stable or increased ascites production rate, documented by an unchanged or shorter time between paracenteses.

Patients with objective response or stable disease (NC) continued therapy until disease progression.

Results

Five of the 23 patients who entered this study received only one cycle of therapy (2 refusals of therapy, 2 lost to follow-up, 1 persistent leukopenia) and were not evaluable for response. The median number of treatment cycles was 2 (range 2–6). Of the 18 evaluable patients, 15 (83%) showed rapidly progressive disease after a median of two cycles of therapy, with median survival time 3.5 months from the start of CTX treatment. Three patients (17%) had stable disease lasting 3+, 4, and 5 months, respectively. No PR was observed.

Three patients were excluded from analysis of toxicity because of inadequate follow-up data. One patient stopped treatment after the first cycle of therapy because of severe leukopenia persisting 5 weeks after the drug administration, together with a drop in performance status. Among the 51 evaluable courses, there were five therapy delays because of WBC counts < 3,000/μl on the day of treatment. No dosage

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modification was required. The median WBC nadir on day 21 was 3,000/μl (1,700–10,700). No thrombocytopenia was seen, with a median platelet count nadir on day 21 being 175,000/μl (102,000–559,000). Anemia, defined as a drop of more than 2 g% from the starting hemoglobin value, was reported in 25% of the patients. As regards non-hematological toxicity, 30% of patients experienced intractable vomiting on the day of drug administration; 25% suffered from nausea and controllable vomiting. Partial alopecia was reported in 30% of patients. No mucositis or cystitis was seen.

Discussion

On the basis of these results it seems that CTX is not effective in ovarian cancer refractory to DDP. Even though the selection of patients for the present study was very unfavorable (residual tumor after primary surgery > 10 cm in 55% of patients, rapidly growing tumors in all cases, short interval from initial diagnosis), the results, 83% progressive disease with no objective response among 18 evaluable patients, suggest there may be cross-resistance between DDP and CTX when used sequentially in ovarian cancer. Nevertheless, the reported activity of DDP in patients refractory to conventional bifunctional alkylating agents [1, 2] suggests a one-directional drug-resistance pattern. Other experimental and clinical studies are needed to clarify this point.

If we had considered this as a phase II study, pretending to ignore that CTX is one of the best drugs available for ovarian cancer, we would have concluded that CTX is inactive in this malignancy. Thus, when a new drug fails to show any benefit in ovarian cancer refractory to previous chemotherapy, it does not necessarily mean that it is inactive in this tumor.

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