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Clinical Trial Summary

Phase II Study of 5-Aza-2′-deoxycytidine in Advanced Ovarian Carcinoma

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5-AZA-2′-DEOXYCYTIDINE (NSD 127716, DAC) differs from the parent compound deoxycytidine by the presence of a nitrogen in the 5 position of the heterocyclic ring. After conversion to the nucleotide form by deoxycytidine kinase, DAC is incorporated into DNA, where it can exert its cytotoxic action either through the inhibition of DNA methylase and DNA hypomethylation, or through the production of alkali-labile sites and loss of DNA integrity [1].

The drug has been shown to be active in murine and human leukemias, the highest antileukemic effect being reported after a prolonged exposure time [2]. The clinical use of continuous infusions, however, was hampered by the chemical instability of the drug and a schedule applying three daily 1-h infusions, separated by intervals of 7 h, was studied in adults with solid tumors [3]. The dose-limiting toxicity was myelosuppression, with delayed leukopenia. The MTD was 100 mg/m^2/infusion and the recommended dose was 75 mg/m^2/infusion × 3, repeated every 5 weeks.

Based on a report of some activity in solid tumors, the Early Clinical Trials Group decided to carry out disease-oriented phase II studies, the results of which have been in part published [4]. The present report focuses on the results achieved in patients with advanced ovarian carcinoma.

MATERIALS AND METHODS

Only previously treated patients with a histological diagnosis of advanced epithelial ovarian cancer were considered eligible for this study. Eligibility criteria also included measurable or evaluable disease with documented progression within the last 2 months, no more than two chemotherapeutic regimens, serum creatinine and bilirubin levels less than 125 and 25 μmol/l, respectively.

DAC vials containing 50 mg lyophilized DAC were supplied by Pharmachemie B.V., Haarlem, The Netherlands. They were reconstituted with 5 ml sterile water for injection. Reconstituted vials were further diluted in 250 ml 0.9% sodium chloride for i.v. injection. DAC was given at a dose of 75 mg/m^2 as a 1 h i.v. infusion, three times on day 1 with intervals of 7 h. The treatment was repeated every 5 weeks.

Drug administration was delayed by 1 week if there was no full hematologic recovery at the time of scheduled retreatment. The dosage was modified according to the lowest value of WBCs and platelets measured weekly during the previous course.

Responses and toxicity grades were defined according to WHO criteria [5]. Only the patients for whom weekly blood counts were available were deemed evaluable for hematological toxicity.

RESULTS

Between October 1986 and March 1988, 27 patients were entered into this study. Three were subsequently defined as not eligible: more than two prior chemotherapeutic regimens: one patient; lack of measurable/evaluable lesions: one patient; too old in age: one patient. Table 1 summarizes the characteristics of the remaining 24 eligible patients. All patients had been pretreated with cisplatin and/or platinum analogues. In 79% of the patients, the

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Table 1. *Characteristics of eligible patients*

Characteristics	No. of patients	Percentage
Total	24	
Median age in years (range)	54 (28–69)	
WHO performance status		
0–1	19	79
2	5	21
FIGO stage		
III	9	37
IV	15	63
Largest tumor diameter		
≤5 cm	9	37
>5 cm	15	63
Previous treatment		
One chemotherapy regimen	8	33
Two chemotherapy regimens	16	67

treatment-free interval between prior chemotherapy and DAC lasted less than 6 months.

Nineteen patients were evaluable for response and toxicity, two for response only and three were not evaluable for any analysis (tumor-related death within the first 4 weeks of treatment: one patient; concomitant radiotherapy: one patient; lost to follow-up: one patient). Nineteen patients showed a tumor progression, which was documented after the first cycle in eight of them while two patients had a stabilization of the disease for 3 and 8 months respectively.

The median number of cycles was two (range 1–5). Nineteen patients were evaluable for hematological toxicity after the first cycle. The median WBC nadir was 0.9 × $10^3/\mu l$ (range 0.2–2.5) occurring on day 23 (range 19–35) and recovering by day 36 (range 23–49). The median platelet nadir was 96 × $10^3/\mu l$ (range 13–322 × $10^3/\mu l$) occurring on day 15 (range 13–22) and recovering by day 23 (range 19 to >33). Grade III–IV leukopenia and thrombocytopenia occurred in 84 and 26% of the patients respectively. Vomiting grade 2 and 3 was reported in 31 and 10% of the cases. One patient developed fever up to 39.6°C and bilateral pleural effusions while in agranulocytosis. At the time of death, which occurred 5 weeks after the treatment, the WBC and the platelet counts were 4.6 × $10^3/\mu l$ and 81 × $10^3/\mu l$. *Post mortem* examination showed extensive bilateral bronchopneumonia, intraperitoneal hemorrhages and intestinal obstruction.

DISCUSSION

The negative results of all the phase II studies done in solid tumors [4] and the objective responses reported in phase I–II studies in leukemias, confirm the good antileukemic activity shown by DAC in murine models and limit its clinical use to the treatment of hematologic malignancies.

Besides the unfavorable characteristics of their disease, the women with cancer of the ovary participating in phase II studies usually have a reduced bone marrow reserve; as observed in the present study, this fact determines a myelosuppression more severe than that suffered by the patients with other solid tumors. The higher risk of toxicity and the low chance of antitumor activity recommend that in pretreated ovarian cancer patients, the phase II studies of new agents should be carefully devised.

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