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Phase II Trial of Bleomycin in Patients with Advanced Ovarian Cancer: an EORTC Gynecological Cancer Cooperative Group Study*

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Abstract—*Bleomycin was administered by continuous i.v. infusion at a dose of* 20 mg/m²/day *for* 7 days *to* 18 *evaluable patients with advanced ovarian epithelial cancer resistant to conventional chemotherapy. The toxicity pattern was no different from that known from earlier studies using continuous infusion of bleomycin with the exception of the occurrence of a life-threatening allergic reaction in one patient, which led to discontinuation of treatment after* 3 days. *Only one patient showed a partial response for* 2 months (5.5%), *indicating that the drug has no significant activity in this unfavorable group of patients.*

INTRODUCTION

BLEOMYCIN has not been adequately tested in patients with ovarian tumors of epithelial origin, although cumulative data do not suggest a high grade of activity [1-9]. This is a report of a phase II study of bleomycin used in a continuous infusion regimen in patients with advanced ovarian carcinomas, resistant to prior conventional therapy.

MATERIALS AND METHODS

Twenty-eight patients with stage III or IV ovarian cancer were entered into this phase II trial. Patient eligibility requirements included: (a) histologically proven serous, mucinous, endometrioid, undifferentiated or mesonephrotic ovarian carcinomas; (b) tumor resistant to known effective agents; (c) measurable disease; (d) age <75 yr; (e) a performance status (P.S.) ⩾ 50 (Karnofsky) and an expected survival >4 weeks; (f) a normal renal and pulmonary function; (g) no chemotherapy or radiotherapy for at least 4 weeks prior to entry on study.

Only 18 patients were fully evaluable. Ten patients were not considered eligible for the study for the following reasons: no clear measurable disease (4), poor general condition (2), age above 75 yr (1), prior chemotherapy within 4 weeks (1); two patients did not receive prior chemotherapy, but received additional chemotherapy within 2 weeks after the administration of bleomycin.

The median age of the 18 evaluable patients was 55 yr (range, 36-71 yr), while the P.S. ranged from 50 to 70 (median, 60). Prior treatment included surgery in all patients ('curative' in six, 'palliative' in ten, unknown in two), radiotherapy in five and chemotherapy in all. Doxorubicin, cyclophosphamide, cisplatin, 5-fluorouracil and melphalan were the most commonly used drugs, either alone or in combination.

Before starting the bleomycin all patients had a complete history and physical examination and a laboratory evaluation including: cbc, 12-channel biochemical screening profile, serum creatinine,

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urinalysis, chest roentgenogram and intravenous pyelogram. Upper gastrointestinal series, barium enemas, bone and liver scans, CT-scan or ultrasound examinations were performed when clinically indicated. All patients had daily examination of the oral cavity for mucositis and chest auscultation during bleomycin administration, weekly physical examination (and measurement of lesions) and cbc during the first month, while the same examinations, biochemical tests and chest roentgenograms were repeated every month thereafter.

The treatment program consisted of bleomycin given at a dose of 20 mg/m^2 daily by continuous infusion for 7 days or until severe toxicity became apparent. In principle, the study was limited to one course of treatment and patients were to be observed until progression of disease did occur.

Response was defined as follows: complete response: disappearance of all detectable disease for at least 1 month; partial response: incomplete disappearance of lesions, judged as a $\geqslant$50% reduction of total initial tumor burden for at least 1 month; progressive disease: appearance of new lesions and/or $\geqslant$25% enlargement of existing lesions; and stable disease: any response not falling into any of the previous categories, including patients with a <50% response.

RESULTS

Fifteen patients received the scheduled 7-day infusion of bleomycin. In one case the drug was discontinued after 3 days because of life-threatening bronchospasm, while one patient received bleomycin at a daily dose of 10 mg/m^2 for 5 days (by error) and the full dose thereafter. A third patient received two courses of bleomycin (17 mg/m^2/day for 7 and 6 days respectively, with an interval of 7 weeks), because of excellent tolerance and a 30% tumor reduction after the first course.

Only one patient could be classified as a partial response (5.5%), with a more than 50% reduction of an abdominal tumor mass for 2 months. Some antitumor effect was observed in another patient, where a 50% decrease in skin nodules was found for 4 weeks, but overall tumor response had to be classified as stable disease. Of the remaining 16 patients, two had stable disease of significant duration (4 and 7 months respectively), six showed no change in tumor lesions for only 1 or 2 months, while in eight patients progressive disease was evident from the start of treatment with bleomycin.

Drug toxicity is summarized in Table 1. The most frequently encountered side-effects were anorexia (67%), fever (67%), nausea and vomiting (50%), mucositis (50%) and alopecia (39%). Anorexia, nausea and vomiting usually started during the first days of bleomycin infusion (days 1-3) and persisted up to the seventh day. Grade II fever (38-40°C) was found in eight patients; the other four patients had only grade I. One patient developed Quincke's edema, skin rash, high fever and severe dyspnea on the third day of treatment, necessitating discontinuation of treatment. This allergic reaction to the bleomycin was successfully treated with high doses of corticosteroids. Hematologic toxicity was mild. In those patients where data on weekly blood counts were available (13) only one showed a WBC count below 4.0×10^9/l (3.7) and two patients showed platelet counts less than 100×10^9/l. However, the latter two patients had low platelet counts at the start of treatment as well (115 and 90×10^9/l). In six patients blood counts were determined on several days during the 7-day infusion period; in four cases mild leukopenia was found ($2.4\text{-}3.6 \times 10^9$/l), while thrombocytopenia was found in three, being 60, 70 and 80×10^9/l.

Table 1. Non-hematological side-effects of bleomycin infusion

	Mild/moderate	Severe	Life-threatening
Anorexia	10	2	—
Drug fever	12	—	—
Nausea/vomiting	9	—	—
Mucositis	6	2	1
Alopecia	4	3	—
Skin	2	1	—
Pain at injection site	2	—	—
Allergic reaction	—	—	1

DISCUSSION

The success obtained with local administration of bleomycin for the control of pleural and peritoneal effusions in a small series of patients with advanced ovarian cancer had been the only positive finding with respect to a possible role of

bleomycin in ovarian epithelial cancer at the time this trial was initiated [2].

In the past systemic use of bleomycin alone or in combination in this disease did not suggest a high grade of activity [1, 3-8]. However, in all of these series only small numbers of patients had been treated and no adequate trial with bleomycin alone had been performed. Only very recently Blackledge *et al.* reported data of a phase II trial of bleomycin alone in patients with advanced epithelial ovarian cancer showing progression after single alkylating-agent therapy [9]. Four out of the 24 patients showed a partial response (17%), and the investigators concluded that the drug deserved further study in this disease. In the latter study 15 mg of bleomycin was given twice weekly by intramuscular route. In the previous studies the drug was given once [3] or twice a week [1,4,6], or daily [1,3,4], and dosages per administration varied from 5 to 40 mg/m^2. Both experimental and clinical studies suggest that bleomycin is more effective when given as a continuous infusion compared to the intermittent schedule [10, 11], but no conclusive data on this superiority are available. The present study, using continuous infusions in patients with ovarian cancer, failed to indicate any significant activity of bleomycin in this disease. However, 14 of the 18 evaluable patients had received more than one drug earlier (median, 4; range, 2-6). Therefore, the negative result in this study does not rule out the possibility of a somewhat higher response rate in non-pretreated patients. It may also explain the different outcome comparing the present study with that reported by Blackledge *et al.*, where patients had received only a single alkylating agent before.

Nevertheless, on the basis of our results we would hesitate to use the drug in first-line therapy. First, bleomycin has not demonstrated much activity against adenocarcinoma of any site in the past [6,12]. Second, in ovarian carcinoma combination regimens including both bleomycin and cisplatin, though showing antitumor activity in second-line treatment, do not seem any better than might have been expected from cisplatin alone, while toxicity is found to be enhanced [13,14].

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