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Phase II study of fotemustine in patients with advanced ovarian carcinoma. A trial of the EORTC Gynecological Cancer Group

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Abstract

30 patients with advanced ovarian cancer, all platinum pretreated, were treated with an induction cycle of fotemustine. Maintenance therapy was given to 6 patients. No objective response was observed among the 21 evaluable patients. The main toxicities were gastrointestinal, with grade 3 nausea and vomiting reported in 40% of the patients, and haematological, with grade 4 leucopenia reported in 2 patients and grade 4 thrombocytopenia in 5 patients. Therefore, no role has been demonstrated in our cohort for the use of fotemustine, a nitrosourea, in pretreated ovarian cancer.

Keywords: Ovarian cancer; Chemotherapy; Nitrosourea; Fotemustine

1. Introduction

Nitrosoureas have been tested infrequently for the treatment of advanced ovarian cancer. Two studies of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in ovarian carcinoma, each with 11 pretreated patients, failed to show efficacy for BCNU in this disease [1,2], and a study of PCNU in ovarian cancer also showed no response [3]. However, in one study, lomustine (CCNU) administered to 13 mainly non-pretreated patients produced a response in 7 patients, including a decrease of ascites [4], and in another study, 7 out of 27 ovarian cancer patients were considered responders [5]. These results were not, however, confirmed by a further study comparing CCNU and methyl-CCNU in 57 pretreated ovarian cancer patients, with no responders being observed [6].

Fotemustine has been developed with an intensive initial dose schedule, and has showed promising results in malignant melanoma, a chemotherapy-refractory disease [7,8], and in uveal melanoma [9] and primary brain malignancy [10,11].

In the current study, for the European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group, fotemustine was tested as second-line treatment in a phase II study in advanced ovarian cancer.

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2. Patients and methods

30 patients with progressive measurable ovarian cancer were entered. 3 patients were found to be ineligible (inadequate performance status) and the results of 6 could not be evaluated (treatment refusals, insufficient treatment, protocol violations). Characteristics of all eligible patients are shown in Table 1. All patients had been pretreated with up to two platinum-containing chemotherapy regimens. Fotemustine was administered intravenously (i.v.) by 1-h infusion at 100 mg/m^2 on days 1, 8, and 15 (induction cycle), followed after a 5–7 week interval by maintenance therapy at 100 mg/m^2 i.v. every 3 weeks. Toxicity and response were assessed by World Health Organization (WHO) criteria. Responses were documented by physical examination, X-rays or computed tomographic (CT) scans on days 21 (3 weeks) and 49 (7 weeks).

The local ethical and/or protocol review committees approved the study, and patients were included only after giving written, or witnessed oral, informed consent.

3. Results

The median number of courses administered was 1 induction cycle. Only 6 patients received maintenance injections (median: 1, range 1–3). No objective responses were observed among the 21 patients who could be evaluated (95% confidence interval (CI) 0–16%). 6 patients were stable 7 weeks after the start of therapy, the median duration of stability being 14 weeks (range 12–17 weeks). 15 patients progressed after a median observation time of 7 weeks (time to progression range: 3–11 weeks). WHO grade 3 nausea and vomiting was reported in 40% of the patients. The median white blood cell nadir was 2.0×10^9/l, range 0.2–4.9×10^9/l, including 2 patients under 1.0 (WHO grade 4 toxicity). The median platelet nadir was 46×10^9/l (range 16–222×10^9), including 5 patients with WHO grade 4 toxicity.

Table 1
Characteristics of eligible patients

Number	27
Median age (years)	60 (38–75)
Performance status	
WHO 0	4
WHO 1	16
WHO 2	7
Prior treatment	
Surgery	26
Platinum chemotherapy	27
Inevaluable	4
Adjuvant	3
Response	9
No response	11
Radiotherapy	2

WHO, World Health Organization.

4. Discussion

In spite of promising activity in other chemotherapy-refractory diseases [7–11], fotemustine has shown no activity in advanced ovarian cancer patients in our cohort. It has previously been postulated that resistance to nitrosurea chemotherapy in ovarian carcinoma may be related to high cellular expression of the ATase protein in these tumours [12], which may be of relevance in this respect. Furthermore, the moderate to severe myelotoxicity of nitrosoureas, as shown by this and other studies [8], means that nitrosoureas are difficult to use at adequate doses in combination therapy. In common with other groups [13], therefore, we conclude that nitrosoureas are of minimal use in the treatment of ovarian cancer.

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