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Phase II Study of High-dose Megestrol Acetate in Patients With Advanced Ovarian Carcinoma

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The EORTC Gynaecological Cancer Cooperative Group conducted a phase II study of high dose oral megestrol acetate: 800 mg/day for 1 month followed by 400 mg/day as maintenance treatment, in heavily pretreated patients with ovarian cancer. Of 72 patients included in this study, 54 were fully evaluable for response and toxicity. The response rate was low with only 1 patient having a partial reponse, 9 patients with stable disease and 44 patients with progressive disease. The toxicity profile was low. However, 1 patient died after 2 months of treatment, and in 3 patients thrombo-embolic events occurred. Weight gain varied in 20 of the 61 patients from 0.5 to 16 kg. This study does not suggest that the overall 10% benefit from hormonal therapy for chemotherapy refractory ovarian cancer will improve by increasing the dose.
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INTRODUCTION

OVARIAN CARCINOMA still remains the most common cause of death from gynaecological malignancies [1].

Chemotherapy has been increasingly utilised as primary treatment for epithelial ovarian tumours because approximately two thirds of women have stage III and IV disease, which is not surgically curable, and even in the 30% of patients who have what appears to be localised (FIGO stage I and II) disease, relapse eventually occurs in approximately 40%. Thus, the vast majority of patients will be candidates for chemotherapeutic management at some point in their disease.

Although highly effective chemotherapeutic regimens can produce durable remissions, most patients cannot be cured. Currently, approximately 30% of patients reach a complete remission and a long therapy-free period, with a good quality of life, after treatment with cisplatin-based chemotherapy [2]. Approximately 70% of the patients relapse.

New alternatives are still badly needed. The search for alternative treatment modalities for ovarian cancer has included hormonal agents; the relatively low toxicity of hormonal therapy making it an attractive approach for palliative treatment.

Animal experiments [3], epidemiological [4, 5] and some clinical data [6, 7] indicate that epithelial ovarian carcinoma can be considered as an endocrine-related tumour. The objective response rate of advanced ovarian carcinoma to hormonal therapy has been modest, 5–20%. These data are in agreement with the results obtained within the EORTC Gynaecological Cancer Cooperative Group (EORTC-GCCG) with both medroxyprogesterone acetate and tamoxifen [6, 8].

Various progestins have been reported to have activity in patients with advanced ovarian carcinoma, but the results are conflicting [6]. From the available data, with in most studies a response rate less than 10%, the superiority of any type of progestin is unproven. Geisler [9], however, suggested that high dose megestrol acetate is more effective than the more commonly used moderate doses of progestins. In that study, the drug was given at a dose of 800 mg/day for 30 days followed by 400 mg/day until disease progression. Patients were considered to be evaluable for response after a treatment period of at least 2 months. 10 of 22 adequately treated patients responded (45%). However, Ahlgren [10] found no response among 30 evaluable patients. Thus, the data are inconclusive for the role of high dose progestin therapy.

Based on the theortical hormone dependency of ovarian epithelial cancer and results from the literature, the EORTC-GCCG performed a phase II study of high dose megestrol acetate in patients with advanced ovarian carcinoma, who were resistant to or relapsed after chemotherapy.

PATIENTS AND METHODS

Patients with histologically confirmed ovarian carcinoma originating from the epithelial surface of the ovary (WHO classification) entered this trial. This classification includes serous, mucinous, endometroid, clear cell and undifferentiated adenocarcinomas. Eligibility criteria included age $\leq$ 80 years, life expectancy of 2 months or more, no prior hormonal therapy and informed consent. Patients had to have measurable and/or evaluable disease outside previously irradiated areas, as well as documented progression after adequate trials with conventional chemotherapy.

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Table 1. Characteristics of eligible patients

Number of eligible patients	67
Age (years)	
Median	62
Range	27–80
Performance status (WHO)	1
Range	0–2
Prior therapy	
Surgery	64
Radiotherapy	7
Chemotherapy	62
Histological diagnosis	
Undifferentiated	4
Adeno	23
Clear cell	2
Endometroid	3
Serous	33
Mucinous	2
Extent of disease	
Intra-abdominal only	38
Extra-abdominal only	7
Intra- plus extra-abdominal	22
Response (n = 54)	
Partial response	1
No change	9
Progressive disease	26
Early progression	14
Early death	4

Treatment consisted of oral megestrol acetate 800 mg/day for 1 month followed by 400 mg/day as maintenance therapy. Patients were evaluable for response if they had been treated for 2 months. Toxicities and responses were defined according to WHO criteria [11]. Early death due to progressive disease was evaluable as treatment failure.

RESULTS

72 patients entered the study. 5 patients were not eligible: 3 with no measurable disease, 1 with all lesions in irradiated areas and 1 with a performance status score above 2. 6 patients were eligible but not evaluable because of insufficient treatment (dose/duration). 7 patients were evaluable only for toxicity because of too short a treatment duration. 54 patients were fully evaluable for response and toxicity (Table 1). One partial response was observed. In 9 patients the disease remained stable, and 44 patients had progressive disease.

Toxicity in 54 fully and 7 partly evaluable patients consisted of nausea/vomiting grade 1 (4 patients), grade 2 (2 patients), grade 3 (1 patient) and grade 4 (1 patient); diarrhoea grade 1 (3 patients). In 1 patient, hair loss (grade 1) was noted that could not be attributed to previous chemotherapy almost 3 years before. One patient had a serious allergic skin reaction preventing further treatment with megestrol acetate. One patient complained of drowsiness. Fluid retention with oedema of the legs and dyspnoea was observed in 2 patients. Overall, 20 of the 61 patients showed weight gain (not related to oedema) varying from 0.5 to 16 kg. In 3 patients, thrombo-embolic events occurred that could effectively be treated. One other patient died after 2 months of treatment with megestrol acetate due to a large myocardial infarction with, at autopsy, a large thrombotic mass in the apex of the heart; there was also progressive disease with multiple metastases in the lungs, liver and para-aortal lymph nodes with extended peritoneal spread.

DISCUSSION

Our study showed that the use of high- dose megestrol acetate was not effective in ovarian cancer patients previously treated with platinum-based chemotherapy. An objective response rate was found in 1 out of 54 patients. In that respect, our study is in agreement with several other reports [6, 12, 13]. Moreover, the number of patients with thrombo-embolic complications was disturbing and might have been related to the dosages used. Apart from the study of Geisler, in which patients were less heavily pretreated, there are no other studies clearly indicating that higher dosages of progestins are needed in these circumstances. Overall, approximately 10% benefit (response) from different hormonal therapies can be expected in refractory ovarian cancer patients, which may be accompanied by subjective improvement, and our study does not suggest that these results will be enhanced by increasing the dose. However, a better selection of patients who might benefit from these treatments is warranted. In that respect, routine receptor status analysis should be considered because the existence of oestrogen and progesteron receptors is suggested to correlate positively with the degree of differentiation and better prognosis of these patients [14].

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