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Phase II Trial of Flutamide in Advanced Ovarian Cancer: an EORTC Gynaecological Cancer Cooperative Group Study

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New active non-toxic therapeutic regimens are warranted in ovarian cancer relapsing after platinum-based chemotherapy. Some investigators have determined that androgen receptors predominated over oestrogen and progesterone receptors in untreated common epithelial ovarian cancer tissue cytosols. In an effort to test its antitumoural activity, 68 pretreated patients with epithelial ovarian cancer were given flutamide 750 mg/day orally for at least 2 months. Of 32 patients who received a minimum of 2 months of therapy, pretreated with at least one platinum-based chemotherapy, and a median of two chemotherapy regimens, two (6.3%) objective responses (one complete and one partial) and nine (28%) disease stabilisations were observed; these lasted 44 and 72 weeks, respectively (for the complete and partial response), and for a median of 24 weeks for stabilisations (range 12–48+). Nausea and vomiting were the most frequent side-effects. These occurred in 19/55 (34.5%) patients evaluable for toxicity. Flutamide has to be considered ineffective in patients extensively pretreated with chemotherapy, and it is not devoid of side-effects.

Key words: epithelial ovarian cancer, phase II, flutamide
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INTRODUCTION

EPITHELIAL OVARIAN cancer is the most frequent cause of gynaecological cancer death, and represents the fourth leading cause of cancer death among women in western countries [1].

The main treatment modality used in the treatment of advanced ovarian cancer is cytoreductive surgery, followed by systemic therapy with platinum-based chemotherapy regimen [2, 3]. Usually these therapies are accompanied by severe toxicities which are very difficult to tolerate, especially in older patients. Therefore, it is necessary to find alternatives to current therapies with new active non-toxic therapeutic regimens. Little is known about the aetiology or pathogenesis of malignant epithelial neoplasms of the ovary, but sufficient evidence indicates that ovarian cancer is an endocrine-related tumour. Epidemiological studies have shown that specific events of the reproductive system, such as early menarche, history of marked dysmenorrhoea and premenstrual tension, infertility problems, nulliparity or a low mean number of pregnancies, first conception at an older age, etc., all correlate with ovarian cancer. Specific steroid receptors have been demonstrated in normal human ovaries and in ovarian cancers [4–8]; this fact, along with animal experiments [9] and some clinical data [10, 11], suggests that ovarian cancer may be susceptible to endocrine manipulations.

Efforts to delineate the precise role of hormonal therapy in the management of ovarian cancer include the empirical use of progestins, oestrogens, anti-oestrogens, androgens, aminoglutethimide and LH-RH (luteinising hormone releasing hormone) agonists [11–21]. The objective response rate of advanced ovarian carcinoma to hormonal therapy has been modest, as seen in previous trials conducted by the EORTC Gynaecological Cancer Cooperative Group [22]. However, the therapy in these cases was mostly used as second-, third- or even fourth-line attempts after the failure of a multidrug chemotherapy. Since the postmenopausal ovary still continues to produce androgens while production of oestrogens and progesterone ceases [23, 24], and since ovarian cancer is more frequent in postmenopausal women, some investigators recently measured androgen receptors (AR) in addition to oestrogen (ER) and progesterone (PgR) receptors [4]. AR (90%) clearly predominated over ER (55%) and PgR (52%) in the 94 untreated common epithelial ovarian cancer tissue cytosols examined. Analysis of ovarian cancer microsomal aromatase activity, which converts testosterone to oestradiol-17β, showed that the enzyme was detectable only in one third of the cases, and that all tumours which were negative for aromatase contained AR [5]. In these aromatase-negative tumours, androgens may not be further metabolised into oestrogens, and tumour cells may be influenced by the androgens through the AR present in them, suggesting that an anti-androgen treatment could possibly benefit patients with such tumours.

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Flutamide (SCH-13521) is a substituted anilide and an oral, non-steroidal anti-androgenic agent which, differently from cyproterone acetate, has been found to be devoid of other hormonal activities (it can be considered a pure anti-androgen). Several experiences have been reported concerning the use of flutamide (usually at the dose of 750 mg/day) in human advanced prostate cancer. In these studies, flutamide alone [25] or in combination with an LHRH agonist proved to be an active drug in this disease, and compared favorably with DES (diethylstilbestrol) or orchiectomy [26]. Flutamide has also been evaluated in postmenopausal patients with breast cancer [27], but did not show any activity in these circumstances [27]. No data are available on the use of flutamide in ovarian cancer patients. Considering the abovementioned data, the EORTC Gynaecological Cancer Cooperative Group decided to start a phase II (EORTC protocol no. 55882) trial in order to study the usefulness of flutamide in patients with advanced ovarian carcinoma.

PATIENTS AND METHODS

Patients with histologically verified ovarian carcinoma (according to WHO classification), with any degree of differentiation, with FIGO stage III, IV or recurrent disease, with documented progression of disease after adequate chemotherapy trials, and with measurable (bidimensionally) or evaluable (unidimensionally measurable) disease were considered eligible for the study. Informed consent was requested.

Conditions for patient ineligibility included: age < 18 years, life expectancy less than 2 months or performance status 4 (according to WHO), brain involvement, previous or concurrent cancer at other sites, malignant effusions as the only disease parameter, and prior treatment stopped within 4 weeks before entering the trial.

Flutamide was administered at a dose of 750 mg/day given orally (one tablet three times daily) for a minimum of 2 months. Assessment of response involved all measureable or evaluable lesions up to a maximum of eight representative lesions. Computed tomography (CT) scanning and ultrasound were accepted as means of measuring indicator lesions. Patients were seen for clinical examination and registration of side-effects on days 15 and 29, and thereafter monthly at the outpatient department. Routine haematological blood tests were performed prior to treatment and repeated monthly. Standard WHO criteria were used to assess response and toxicity. Patients were considered evaluable for response if they were treated for a minimum of 2 months, unless this was clearly not in their best interest, or if they had early progression.

RESULTS

From April 1989 to April 1990, a total of 68 patients entered the trial in 18 institutions. 62 out of 68 entered patients were considered eligible. The remaining 6 patients were ineligible for the following reasons: 2 patients had no measurable lesions, 1 patient had no progressive disease, 1 patient had incorrect histology, 1 patient had a second malignancy (breast cancer), and 1 patient had insufficient data. Only 32 patients completed the 2-month therapy with flutamide. 30 patients discontinued treatment before the end of the requested minimal treatment duration of at least 2 months: 22 patients for rapidly progressive disease, 7 patients due to early death (in 5 patients due to malignant disease, and in 2 patients due to cerebrovascular attack and a probable pulmonary embolism, respectively) and 1 patient had inadequate follow-up.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	62
Age (years)	
Median	60
Range	31–86
WHO performance status	
0	16
1	29
2	17
FIGO stage at diagnosis	
I	2
II	8
III	41
IV	11
Histological type	
Serous	33
Mucinous	4
Clear cell	1
Endometrioid	1
Unclassified	
Adenocarcinoma	22
Undifferentiated	1
Prior treatment	
Surgery	58
Chemotherapy	62
No. of prior regimens	
Median	2
Range	1–4

Patients' characteristics (excluding the 6 ineligible patients) are shown in Table 1. All patients were refractory to or relapsing after platinum-based chemotherapy. The median number of prior chemotherapy regimens was two (range one to four). As described in Table 2, only 2 patients showed an objective response (one complete, lasting 44 weeks and one partial, lasting 72 weeks; the histology for both patients was serous cystadenocarcinoma). 9 patients showed disease stabilisation with a median duration of 24 weeks (range 12–48+), 21 patients had progressive disease and early death was recorded in 5 patients due to early progression. Drug-induced toxicity could be evaluated in 55 patients and is summarised in Table 3. Only in 2 cases was treatment stopped because of excessive nausea and vomiting due to flutamide.

DISCUSSION

Our study indicates that flutamide is only marginally active in patients with advanced ovarian epithelial cancer, who are beyond

Table 2. Therapeutic activity

	No. of patients
Complete response	1
Partial response	1
No change	9
Progression	21
Early death (progression)	5
Early death (other)	2
Not evaluable	23
Total	62

*Table 3. Non-haematological toxicities in 55 patients**

	G1–G2	G3
Nausea and vomiting	17	2
Diarrhoea	1	1
Constipation	4	—
Dizziness	2	—
Insomnia	1	—
Taste alteration	1	—
General depression	—	1
Somnolence	1	—
Headache	1	—
Tiredness	2	1
Hot flushes	1	1
Pulmonary embolism	2	—
Anorexia	1	1
Thrombosis	1	—

*12 Patients presented more than one toxic symptom

the stage of conventional chemotherapy or resistant to it. Only 2 patients responded, i.e. 6.3% (95% confidence intervals 1.7–20.2%) of all patients considered to have had an adequate trial (≥ 2 months therapy) or 3.2% of all eligible patients. However, 9 additional patients had stable disease for a median duration of 24 weeks (i.e. 28% of all evaluable patients, 14.5% of all eligible patients). These figures are in line with recently published data on cyproterone acetate [28], literature data on other hormone therapies [29], and our own experience with different hormonal agents [22], indicating that only a small subset of patients may benefit from such treatments in these circumstances.

Unfortunately, a large number of patients (48%) did not complete the planned 2 months of therapy because of early progressive disease. Ideally, these hormonal agents should be tested earlier in the course of the disease. For obvious reasons, this will not be possible as first-line in the majority of patients with advanced disease because of the high response rate of platinum-based combination chemotherapy. Responses to hormonal therapies are predominantly observed in patients with serous cystadenocarcinomas or more so with endometrioid tumours of the ovary [11, 30], and in patients receiving hormonal treatment either in first-line or after only single-agent non-platinum chemotherapy. Recurrent tumours and metastatic disease seem to contain fewer oestrogen and progesterone receptors than primary tumours [30, 31]. It should be emphasised that in this study, as in many others reported in the literature, the androgen receptor status is unknown. For this reason, questions regarding the role of androgen receptors and anti-androgen therapy in ovarian cancer remain so far unanswered. To better define the role of flutamide in ovarian cancer, studies using this agent after first-line chemotherapy in patients with known androgen receptor status should be performed. As of now, though, flutamide is considered ineffective in patients extensively pretreated with chemotherapy, and it is not devoid of side-effects.

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Prognosis and Treatment of T1G3 Bladder Tumours. A Prognostic Factor Analysis of 121 Patients

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Patients with T1G3 bladder cancer have a considerable risk for recurrence and/or progressive disease. Until now no consensus has been achieved on the optimal treatment. Within the Dutch South Eastern Bladder Cancer Study Group, 155 patients with a T1G3 bladder tumour were seen between 1983 and 1988. After review of histology, 121 could be evaluated and recurrence-free interval was studied with regard to prognostic factors. Prognostic factors such as sex, age, blood group, abnormalities on intravenous urography, pretreatment tumour configuration, number of tumours, number of locations involved in the bladder, voided urine cytology, results of random biopsies and mitotic index were evaluated, using a multivariate analysis with the Cox proportional hazard model. During the follow-up period, 70 (58%) patients had recurrent bladder cancer, and of these 30 (43%) had progression into invasive disease. Of the possible prognostic factors analysed, only multiplicity ($P = 0.03$) and the number of locations of the tumours ($P = 0.03$) were independent prognostic factors in relation to the risk of recurrence. The recurrence-free interval was influenced by the therapy. For T1G3 tumours, additional intravesical immunotherapy/chemotherapy or radiotherapy after transurethral resection (TUR) increased the recurrence-free interval significantly. Because most other parameters did not show additional prognostic value, the T1G3 tumours can be considered as homogeneous with regard to prognosis. Only multiplicity and the number of locations involved added to the prognostic significance of patients with these bladder tumours. In addition, it is advisable to give patients with T1G3 tumours additional treatment after the initial TUR.

Key words: bladder tumours, superficial, prognosis, treatment
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INTRODUCTION

THE CLINICAL course of superficial bladder tumours (Ta-T1, G1-3, Tis) is characterised by its unpredictability. Although it is obvious that the strategy of treatment differs from muscle-invading bladder cancers, no consensus has been reached about their therapy [1]. Transurethral resection (TUR) of all visible tumour remains the cornerstone of treatment, but the initial TUR is followed by a heterogeneous therapy schedule [1, 2]. Different forms of adjuvant treatment have become available in the last decades. Developments in intravesical chemotherapy