Treating Relapsed Epithelial Ovarian Cancer with Luteinizing Hormone-Releasing Agonist (Goserelin) after Failure of Chemotherapy

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Abstract

Background: The treatment of patients with recurrent ovarian carcinoma after failure of first and second-line chemotherapy is still debated. Chemical agents used for third and fourth-line therapy usually yield poor results with severe toxic side effects.

Objective: To summarize our experience with goserelin in the treatment of patients with recurrent ovarian cancer.

Methods: From September 1996 to June 1999 we administered goserelin, 3.6 mg subcutaneously every 4 weeks, to 15 patients with advanced and recurrent epithelial ovarian cancer (median age 59.0, median performance status 3.0).

Results: Seven of 15 eligible patients relapsed after platinum-based chemotherapy (3 of them also received paclitaxel and another 2 received tamoxifen). Four patients relapsed after carboplatin and paclitaxel, one of whom was treated with topotecan thereafter. Two patients relapsed after single-agent paclitaxel. Two patients with advanced disease and poor performance status without previous treatment received only goserelin. There was one complete response (6.7%) and 1 partial response (6.7%) lasting 8 and 14 months respectively (overall response rate 13.4%). In addition, the disease stabilized in three patients (20%) for a median of 7.5 months. In 10 patients the disease progressed. There was no significant toxicity. Median survival of all patients was 5.8 months.

Conclusion: Goserelin was helpful in one-third of our patients with advanced and refractory ovarian cancer. It is an easy and non-toxic option for treating very ill or previously heavily treated patients.

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Long-term survival of women with advanced epithelial ovarian cancer remains poor, despite high response rates achieved with single-agent or combination platinum and paclitaxel chemotherapy [1–4]. Other agents used for second or third-line treatment after relapse yield a 14–40% response rate [5]. The choice of a specific regimen in the second-line setting is largely a matter of personal preference.

The presence of sex steroid hormone receptors and gonadotropin-releasing hormone receptors in epithelial ovarian tumor cells was demonstrated in several studies. The proportion of positive estrogen receptors in epithelial ovarian cancer is 33–53% and of positive progesterone receptors 20–50% [6,7]. The functional *in vivo* importance of this range of receptor expression is uncertain. Hormonal therapy, e.g., tamoxifen, has yielded variable and generally poor clinical responses [8].

Goserelin is a synthetic luteinizing hormone-releasing hormone agonist. It suppresses circulating levels of luteinizing hormone, follicle-stimulating hormone, testosterone, androstenedione and estradiol in postmenopausal women [9]. Goserelin might be expected to exert its antiproliferative effect in epithelial ovarian cancer either due to a direct action on tumor cells via GnRH receptors, and/or secondary to its ability to lower circulating estrogen and androgen levels by suppression of secretion by ovarian tumor cells [10]. Lind et al. [10] reported two partial responses and five disease stabilizations in 30 patients treated with goserelin who were heavily pretreated. Because of the difficulty in treating women with recurrent ovarian cancer who failed one or more chemotherapy agents, we conducted a pilot study using goserelin in women with advanced ovarian cancer.

Patients and Methods

Our study was conducted between September 1996 and June 1999 in 15 women with recurrent ovarian cancer. These women included patients who: a) had relapsed following at least two lines of chemotherapy, b) were considered too ill to receive or to continue to receive chemotherapy, or c) refused to continue chemotherapy for any reason. All had histologically or cytologically proven epithelial ovarian cancer. All patients had normal blood count, liver and kidney function tests. Disease was evaluated clinically and by ultrasound or computerized tomography. No age or performance status limit was imposed. CA-125 measurements were performed before treatment and once a month thereafter. Of these 15 patients 11 had received platinum or carboplatin-containing chemotherapy previously [Table 1]. Nine patients also received paclitaxel, and four received cyclophosphamide. Two patients received prior endocrine therapy with tamoxifen, and one patient received topotecan. Two patients were treated with goserelin as first-line therapy because of their poor performance status.

Patients were treated with monthly goserelin 3.6 mg subcutaneously. Treatment was continued until disease progression. Disease status and response were evaluated by clinical examination, sequential CT scanning and CA-125 measurements. Response was classified as complete response and partial response, stable disease and progressive disease. The standard response criteria were determined according to World Heath Organization criteria.

GnRH = gonadotropin-releasing hormone

Results

The median age of the 15 patients treated was 59 (range 38–86 years), and their median performance status was 3.0 (range 2–4). Eight patients had serous cystadenocarcinoma, two had mucinous carcinoma, and three had undifferentiated carcinoma [Table 1]. Previous chemotherapy included one or two regimens of cisplatin plus cyclophosphamide in seven patients (three of them also received single-agent paclitaxel, and two received tamoxifen); carboplatin plus paclitaxel in four patients (one was treated with topotecan and three with cyclophosphamide thereafter); and-single agent paclitaxel in two patients, one of whom also received cyclophosphamide. Two patients were very ill and had not received any previous chemotherapy. Tumor site was abdominal with pelvic spread in 10 patients (2 of them with pleural effusions), liver metastases in 2 patients, lung metastases in 2 patients, and liver and lung metastases in 1 patient. Five of the 15 patients also had ascites.

Patients received a median of 5 cycles (range 2–14) of goserelin. Objective response was 13.4%. There was one (6.7%) complete responder: this 59 year old woman had advanced ascites and was bedridden for more than 90% of the time. Chest and abdominal CT showed huge ascites, peritoneal spread and a solid mass in the left ovary. Mammography and gastrointestinal analysis were normal. CA-125 was 500 units/ml. An abdominal puncture was performed. Cytologic examination of the ascites revealed serous ovarian cystadenocarcinoma cells. The patient was known to have diabetes mellitus and hypertension. After four courses of goserelin treatment she achieved a clinically complete remission. CA-125 decreased to 28 units/ml, and her abdominal CT scan showed no evidence of disease. She was in complete remission for 8 months. Thereafter her disease recurred, and after two additional goserelin cycles she died with peritoneal spread after cardiovascular attack. One patient (6.7%) achieved a partial response lasting 14 months. This patient had lung metastases and abdominal disease. Four years previously she underwent TAH + BSO for stage IIb undifferentiated carcinoma of ovary. She received six courses of cisplatin and cyclophosphamide. Lung and abdominal metastases were diagnosed 10 months prior to goserelin treatment. She received treatment with carboplatin and paclitaxel and achieved minimal response for 8 months. After progression, the patient received cyclophosphamide for 2 months. Treatment was stopped because of deterioration in her general condition and she subsequently responded to treatment with goserelin. Response was evaluated by repeated CT scans. In three patients (20%) the disease stabilized for a median of 7.5 months. In the other 10 patients (66.6%) the disease progressed.

There were no severe toxicities related to goserelin treatment. One patient complained of hot flashes, and one had mild transient nausea after the first injection. The median survival of all treated patients was 5.8 months.

Table 1. Characteristics of 15 patients with epithelial ovarian cancer

	N
Age (yr)	
Median	59.0
Range	38–86
Performance status*	
Median	3.0
Range	2–4
Histology	
Serous	8
Mucinous	2
Endometrioid	1
Mixed	1
Undifferentiated	3
Grade	
Well-differentiated	2
Moderately differentiated	4
Poorly differentiated	9
Site of disease	
Abdomen and pelvis	6
Abdomen, pelvis & ascites	2
Abdomen, pelvis, pleural effusion & ascites	1
Abdomen, pelvis, pleural effusion	1
Liver & ascites	1
Liver	1
Lung, liver & ascites	1
Lung	2
Prior therapy	
Median	2
Range	0–4
Crisplatin and cyclophosphamide	7
Carboplatin and paclitaxel	4
Single-agent paclitaxel	5
Single-agent cyclophosphamide	4
Topotecan	1
Tamoxifen	2
None	2

Discussion

The optimum treatment of patients with recurrent disease remains a major management problem in ovarian cancer. Subsequent treatment is based on the timing and nature of the relapse and extent of prior therapy [5]. Most authors agree that patients who respond to initial therapy and relapse more than 6 months later have disease that is most likely still sensitive to prior drugs. Patients with tumor progression during treatment, or who have disease that is likely resistant to the initial drugs, should receive alternative drugs [11]. Most drugs used in the treatment of recurrent disease are platinum agents and paclitaxel as single agents or in combination in drug-sensitive patients, with a response rate of 30–40% [12]. In the management of drug-resistant patients and after failure of repeated chemotherapy in drug-sensitive patients, there is no consensus as to what drug to use as second-line therapy. No studies of combination chemotherapy have been conducted, and single-agent therapy is generally chosen. Several new agents have shown substantial activity in the treatment of patients with recurrent ovarian cancer. These drugs include oral etoposide, docetaxel, topotecan, vinorelbine, liposomal doxorubicin, gemcitabine and tamoxifen, with response rates of 13–30% [13–19].

Patients who were previously heavily dosed with chemotherapy and have disease progression or recurrence are incurable by other

means and would be expected to have a poor response to second and third-line cytotoxic treatment. In these patients, palliation is the goal. The GnRH analogues provide a novel approach to treatment. Kavanagh et al. [20] achieved a 17% partial response rate in 23 patients with advanced epithelial ovarian cancer who were treated with leuprolide (LHRH agonist). All patients had been previously treated with chemotherapy. In a study by Bruckner and Motwani [21], five patients were treated with leuprolide and megestrol acetate and four of them achieved an objective response.

Ginopoulos et al. [22] used goserelin in 38 patients with progressive ovarian cancer under conventional second-line treatment; 4 patients showed a partial response and 8 showed disease stabilization. Remission was sustained for 5–16 months in responding patients. Savelda and associates [23] used goserelin 3.6 mg once a month to treat 23 patients with ovarian cancer progressing on second or third-line polychemotherapy. Partial responses lasting for 4, 8, 10 and 23 months were seen in four patients (17.0%) respectively. Other studies that used goserelin to treat advanced ovarian cancer reported similar response rates [24,25].

In our study, goserelin was used once every 28 days. All patients had very advanced ovarian cancer and most patients (13 of 15) were previously heavily treated. One patient achieved partial response after second-line treatment. One patient without previous therapy achieved complete response for 8 months; this patient was very ill and could not receive any chemotherapy. After remission her performance status was also improved. The overall objective response rate was 13.4%. Three patients (20%) had disease stabilization for a median of 7.5 months. The results of this phase II prospective study are similar to the results reported in other studies. However, to our knowledge, the case of complete remission achieved in our study is the first to be reported in the literature.

In conclusion, goserelin used in the treatment of advanced and refractory epithelial ovarian cancer provides comparable results without significant side effects, and may be considered as an alternative to palliative chemotherapy in advanced disease and in very ill patients who cannot tolerate chemotherapy.

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LHRH = luteinizing hormone-releasing hormone

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