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Report

D-TRP-6-LHRH (Triptorelin) is not effective in ovarian carcinoma: an EORTC Gynaecological Cancer Co-operative Group Study

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Between March and September 1988, 74 patients with progressive ovarian cancer after prior platinum-based therapy were treated with the luteinizing hormone-releasing hormone (LHRH) agonist Triptorelin (Decapeptyl°). Treatment consisted of i.m. injection of 3.75 mg of microencapsulated Triptorelin on days 1, 8 and 28 followed by 4-weekly injections until tumor progression. No objective responses were observed. Eleven out of 68 evaluable patients (16%) had stable disease. The median progression-free survival was 5 months in patients with disease stabilization and 2 months for all evaluable patients. The median survival for patients with disease stabilization was 17 months, whereas for all patients it was 4 months. The treatment was well tolerated; the only reported adverse events were incidental hot flushes. This study showed that the LHRH agonist Triptorelin has only modest efficacy in patients pretreated with platinum-containing chemotherapy. [© 2001 Lippincott Williams & Wilkins.]

Key words: Hormonal therapy, luteinizing hormone-releasing hormone, ovarian cancer, Triptorelin.

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Introduction

In the 1980s no effective second-line therapy was available for patients with progressive ovarian cancer after platinum-based chemotherapy. Several antitumor drugs and endocrine therapy have been investigated. Hormonal therapies, using antiestrogens, progestogens and their combinations, have demonstrated only a marginal or modest effect.[1]

For many years it has been suggested that luteinizing hormone-releasing hormone (LHRH) agonist inhibit proliferation of ovarian cancer by suppressing endogenous gonadotropins,[2,3] which were considered to be mitogenic in this malignancy.[4,5] Recent experimental and clinical data have made this hypothesis questionable.[6] During the past few years, a large body of experimental evidence has emerged indicating that LHRH agonists directly inhibit proliferation of ovarian cancer through LHRH receptors expressed by 80% of these tumors.[7–12]

The former experimental antitumor effects have stimulated the study of the possible role of LHRH agonists in patients with advanced ovarian cancer. The objective of the present study was to determine the

objective response rate and the response duration produced by D-Trp-6-LHRH (Triptorelin), a LHRH analog, in patients with progressive epithelial ovarian cancer after prior platinum-based therapy.

Patients and methods

Eligible patients were women with progression of a histologically proven epithelial ovarian carcinoma after prior platinum-based chemotherapy. Informed consent was given according to the rules of the participating institutes. Exclusion criteria included previous or concomitant second malignancy (except carcinoma *in situ* of the cervix or basal cell carcinoma), malignant effusion as the only disease parameter and a treatment-free interval of less than 4 weeks. Between March and September 1988, 74 patients were included. Pretreatment and follow-up investigations included: general and gynecological examination, complete blood cell counts and differential, blood chemistries, urinalysis, chest X-ray, and CT scan and/or ultrasonography of the abdomen–pelvis. Response evaluation was performed every 2 months. Treatment consisted of an i.m. injection of 3.75 mg of microencapsulated Triptorelin on days 1, 8 and 28, followed by 4-weekly injections until progression.

World Health Organization (WHO) criteria were adopted for the response evaluation.[13] The response duration was dated from the initiation of treatment until documented progression. Survival time was defined as the period between the start of the Triptorelin treatment until death or the last follow-up. Only patients with treatment lasting at least 2 months or with early progression were evaluable for response. This study was updated in December 1999.

Table 1. Eligible patient characteristics

Patients entered/eligible	74/69
Age (years): median (range)	57 (42–87)
Performance status (WHO): median (range)	1 (0–3)
Initial stage (FIGO): no of patients	
I	6
II	5
III	52
IV	6
Histology: no of patients	
serous	19
mucinous	4
clear cell	2
endometrioid	5
mixed	1
undifferentiated	5
papillary	6
unspecified	27
Prior therapy: no of patients	
chemotherapy (platinum based)	69
no of previous chemotherapy regimens	
1	15
2	38
3 or more	16
response to chemotherapy	42
radiotherapy	10
hormone therapy	4
Interval (months) from last treatment	
$\leqslant 4$	42
4–12	23
>12	4

Results

Five patients out of 74 patients were ineligible; three patients had no measurable disease and two patients had another malignancy (an endometrial cancer and a second histologic subtype of ovarian cancer). All eligible patients were evaluable for tumor response except one who never started treatment. Patients received Triptorelin during a median duration of 2 months (range 1–21 months). The characteristics of the eligible patients are presented in Table 1. There were no objective responses, but 11 out of 68 patients (16%) had stable disease with a median duration of 6 months (range 3–21 months). Their progression-free survival and overall survival were median 5 months (range 3–21 months) and 17 months (range 7–123 months) respectively. The characteristics of the patients with disease stabilization are presented in Table 2. The longest stabilization (21 months) occurred to a patient with a single pelvic mass, who benefited from complete resection of the tumor after 13 months of treatment. She is still alive without evidence of disease after a follow-up of 123 months. For all evaluable patients, the progression-free survival and overall survival were median 2 months (range 1–21 months) and 4 months (range 1–123 months) respectively. Sixty-one (88.4%) patients were evaluable for toxicity. The drug was well tolerated. Only transient mild flushes were reported in two patients and transient moderate headaches were reported in two other patients.

Discussion

In the 1980s no effective salvage therapy was available for patients who had platinum-resistant ovarian cancer. Moreover, at this time, retreatment with a platinum-containing regimen in patients with platinum-sensitive disease who experienced a recur-

Table 2. Characteristics of patients with stable disease

Patients with stable disease/eligible	11/69
I	1
II	2
III	8
IV	0
Histology: no of patients	
serous	6
mucinous	0
clear cell	1
endometrioid	0
mixed	0
undifferentiated	4
unspecified	11
Prior therapy: no of patients	
chemotherapy (plantinum based)	11
no of previous chemotherapy regimens	
1	2
2	7
3 or more	2
response to platinum-based chemotherapy	6
progressive disease on platinum	2
stable disease on platinum	3
Interval (months) from last treatment:	
median (range)	3 (1–16)

rence more than 6 months after discontinuation of a platinum-based regimen was not a 'standard attitude'.

A few phase II studies evaluated the direct antiproliferative effect of LHRH analogs in conventional doses in relapsed ovarian cancer, mostly refractory to platinum.[14–23] They involved a limited number of patients. They reported objective response rates of 0–12% and disease stabilization rates of 11–60% with short duration of responses (6–23 months) and median survival time in the range of 6 months. Toxicity was low or absent.[14–23] This study is the largest reported series of LHRH agonist. No responses were observed. Only 16% of patients had disease stabilization. The median progression-free survival was 5 months in patients with disease stabilization and 2 months for all evaluable patients. The median overall survival for patients with disease stabilization was 17 months, whereas for all patients it was 4 months. One patient with a complete resection of the pelvic recurrence during therapy is still alive without evidence of disease after 123 months.

These results show that Triptorelin might be beneficial for patients with disease stabilization, but overall efficacy of this hormonal therapy is low. The development of new LHRH analogs such as potent antagonists[24] or of LHRH analogs containing cytotoxic radicals[6,25] might permit a better use of these drugs in the future.

In conclusion, the LHRH analog Triptorelin has only minor efficacy in patients pretreated with platinum-containing chemotherapy.

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