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Original Research

Clinical benefit of hormonal therapy in advanced ovarian cancer

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Summary

Objectives: To evaluate the benefit of hormonal therapy in advanced ovarian carcinoma. *Materials and Methods:* The present authors reviewed the data of advanced epithelial ovarian cancer patients who underwent hormonal therapy between 2009 and 2016. Primary endpoint was clinical benefit. Secondary endpoints were overall response rate, CA 125 response, overall survival, progression-free survival, and toxicity. *Results:* The authors identified 47 patients. Median age was 61 years. Serous carcinoma was the main histologic subtype (70%). Hormone receptor expression was positive in 23% of patients. Previous to hormonal therapy, 60% of patients were treated with two or more chemotherapy regimens (range 2-8). Hormonal therapy was initiated in 34% of patients due to disease progression and the remaining as maintenance therapy. No relevant toxicity was reported. Progression-free survival was six months (CI 95% 2.1-9.9) and overall survival was 22 months (CI 95% 13.0-31.0). Based on imaging response criteria, one patient had complete response, 70% had stable disease, and 19% progressed on the first evaluation. Overall clinical benefit was 72%. *Discussion:* Clinical benefit was superior to the reported in the literature, probably related to its maintenance use between chemotherapy treatments. More prospective studies are needed to determine the real advantage of hormonal therapy in advanced ovarian cancer *vs.* clinical surveillance, mainly in the maintenance setting, as well as its correlation with hormone receptor expression.

Key words: Ovarian cancer; Hormonal therapy; Letrozole; Tamoxifen; Megestrol.

Introduction

There were an estimated 65,538 new cases of epithelial ovarian cancer (EOC) and 42,716 deaths from this disease in Europe in 2012 [1]. Ovarian cancer remains the leading cause of death due to gynecologic cancer. This cancer is predominantly a disease of older women, with a median age of 63 years at diagnosis. About two-thirds of EOC patients present with late stage disease [International Federation of Gynecology and Obstetrics (FIGO) Stages III and IV]. Five-year survival rate among women with regional and distant disease are 73% and 29%, respectively [2].

Management of advanced EOC consists mainly of primary cytoreduction along with platinum-based chemotherapy. Although up to 70% of patients respond to platinum-based chemotherapy, disease will ultimately relapse [3]. Disease remission can be achieved if treatment with systemic chemotherapy is accomplished, but with progressively shorter treatment intervals and increased treatment-related toxicity [4-6]. Alternative treatment modalities with clinical benefit and minimal toxicity are needed for this population.

Estrogens are implicated in the etiology of EOC. Additionally anti-estrogens can inhibit proliferation of estrogen receptor (ER) positive ovarian cancer cells in vitro, and in vivo [7, 8]. Tamoxifen is an antiestrogen that blocks the ER pathway and aromatase inhibitors inhibit the synthesis of estrogen [9]. Both have been studied in recurrent disease, mainly in the platinum-resistant setting. The evidence in ovarian cancer comes from various phase II studies [10-17]. Results have been modest regarding response rates and correlation to ER and/or progesterone receptor (PR) expression is uncertain [11-13, 16, 18]. Low-grade serous carcinoma (LGSC) are a subset of patients characterized by the indolent behavior and chemoresistance, resembling the behavior of luminal breast cancers [19-21]. Literature is scarce regarding effectiveness of hormonal therapy on this subset of patients. A recent study has revealed advantage of hormonal maintenance therapy compared to observation in women with low-grade serous carcinoma [22].

Materials and Methods

The authors present a retrospective single center study. All advanced EOC patients treated with hormonal therapy between November 2009 and November 2016 in a comprehensive cancer center were included, with review of medical records.

Primary endpoint was clinical benefit rate (CBR). Secondary endpoints were overall response rate (ORR), CA 125 response, overall survival (OS), progression-free survival (PFS), and toxicity according Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Response Evaluation *Criteria* in Solid Tumors (*RECIST*) version 1.1 determined imaging tumor response. Descriptive analysis of main demographic and clinical characteristics was performed. CBR was defined as the percentage of patients with response (partial or complete) and stable disease. CA 125 response was assessed by Gynecologic Cancer Intergroup (GCIG) serum CA 125 criteria. Response assessment and survival data were calculated for first-line hormonal therapy for patients with more than one hormonal treatment. OS was calculated from diag-

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Table 1. — *Baseline characteristics (n=47).*

Median age (range, years)	61 (37-84)
Histological subtype (n, %)	
High-grade serous	20 (42)
Low-grade serous	6 (13)
Serous, NOS	7 (15)
Other histologies	9 (19)
Unknown	5 (11)
Menopausal status (n, %)	
Postmenopausal	35 (74)
Premenopausal	3 (6)
FIGO staging at diagnosis (n, %)	
I	3 (6)
II	1 (2)
III	32 (68)
IV	10 (21)
Unknown	1 (2)
Hormone receptor expression (n, %)	
Positive	11 (23)
Unknown	36 (77)
First treatment (n, %)	
Primary surgery	29 (62)
Primary chemotherapy	12 (25)
Palliative chemotherapy	6 (13)
Prior CT, number of lines (n, %)	
1-2	34 (72)
3-4	9 (19)
≥ 5	4 (9)
Platinum-sensitivity (n, %)	
Platinum-sensitive	31 (66)
Platinum-resistant	16 (34)

nosis until death from any cause. PFS was defined as time from hormonal therapy beginning to disease progression or death from any cause. Patients who were still alive/without progressive disease at the time of analysis were censored on the date of their last follow-up. PFS and OS were evaluated using the Kaplan-Meier method and PFS compared across two groups using the log-rank test. Local institutional Ethical Committee approved this study.

Results

A total of 47 EOC patients were included in this study. Patients' baseline characteristics are summarized in Table 1. Median age was 61 (range 37-84) years, and 35 (74%) patients were postmenopausal. The majority were serous carcinoma histological subtype (n=33), 20 (42%) patients being high grade and 6 (13%) were low grade. Data on hormone receptor expression was available for 11 (23%) patients; all tested positive for ER and eight (17%) were considered PR positive. Median number of previous chemotherapy lines was two. Platinum sensitive disease were predominant, present in 31 (66%) patients. Hormonal therapy was initiated as a new line of treatment in 16 (34%) patients after progression in previous chemotherapy and for "maintenance" treatment in 31 (66%) patients with persistent disease after chemotherapy. Most patients underwent letrozole (36, 77%). No relevant toxicity was reported. Hormonal therapy details are presented in Table 2.

Table 2. — *Hormonal therapy: disease setting, hormonal agent, and patients' performance status (n=47).*

Disease setting?	
"Maintenance" after chemotherapy	31 (66%)
After progression on previous chemotherapy	16 (34%)
Hormonal therapy	
Letrozole 2.5 mg per day	36 (77%)
Tamoxifen 20 mg per day	8 (17%)
Megestrol acetate 160 mg per day	3 (6%)
Performance status (ECOG)	
0-1	33 (70%)
2-3	12 (26%)
Hormonal therapy toxicity	Null

Regarding imaging response, 43 patients were assessed (Figure 1). Clinical benefit rate was 72% and ORR 2%. One complete response was reported for a patient under megestrol with clear cell histology and carcinomatosis, which was maintained for a period longer than five years. Stable disease was the best overall response for 33 (70%) patients and 9 (19%) progressed. Concerning CA 125 response, 39 patients were evaluable for analysis (Figure 2). Two (4%) patients had a CA 125 response, both with radiological stable disease. No response was found for 12 (26%) of patients. Median PFS was six months (CI 95% 2.1-9.9). Median OS was 22 months (CI 95% 13.0-31.0). Median PFS was higher in low-grade serous carcinoma subset of patients (ten months) compared to other histologies (six months), but this difference was not statistically significant ($p = 0.559$). Median OS was similar among high and low grade serous carcinoma (22 months).

After progressing on hormonal therapy, 39 patients received further treatment. Of those 25 (64%) were treated with chemotherapy [median number of lines 2 (range 1-5)], eight (21%) had additional hormonal therapy, and six (15%) were proposed to receive best supportive care.

Discussion

In this study patients with advanced EOC were submitted to hormonal therapy in different disease settings, as a new line of treatment after previous progression and as "maintenance" treatment in patients with disease persistence under chemotherapy. Common studies evaluate patients only in the first setting. In phase II trials with tamoxifen treatment, objective responses and stable disease were seen in 3-7% and 19-38% of patients, respectively [12, 15, 17]. A Cochrane Database Systematic Review of tamoxifen for recurrent ovarian cancer based on non-comparative studies, included 623 patients and demonstrated an ORR of 10% (range 0-56%) and a disease stabilization rate (DSR) of 32% (range 0-83%) [23]. For aromatase inhibitors, studies reported similar ORR and DSR of 0-15% and 17-42%, respectively [10, 11, 13, 14, 16, 24]. A recent retrospective study compared tamoxifen and letrozole in

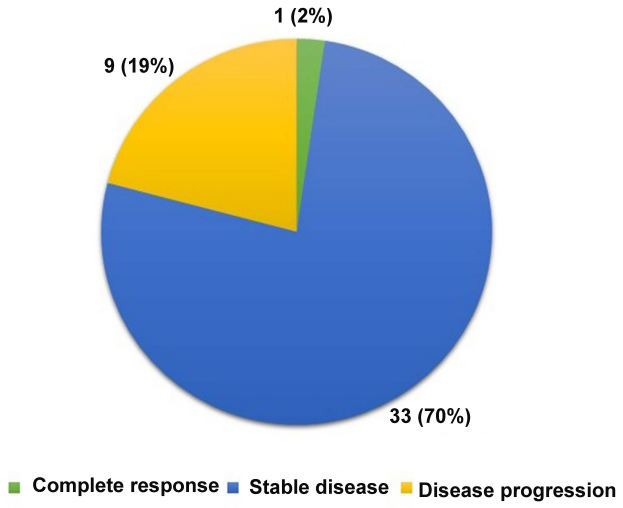

Figure 1. — Imaging response according to Response Evaluation *Criteria* in Solid Tumors (*RECIST*) version 1.1 in ovarian patients who underwent hormonal therapy (n=43). Clinical benefit rate (CBR): 72%; overall response rate (ORR): 2%.

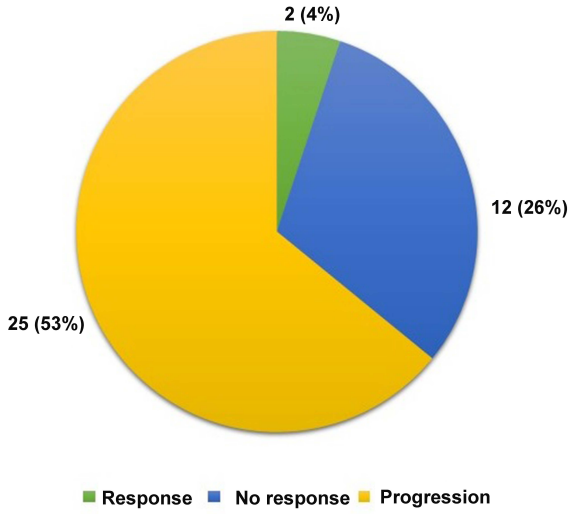

Figure 2. — CA 125 response according to Gynecologic Cancer Intergroup (GCIG) criteria (n=39).

patients with advanced high-grade EOC, with significant difference in ORR or CBR, although responders to letrozole had significantly longer responses (26 *vs.* 11.5 months) [25]. Data on efficacy of megestrol are limited, with ORR of 1-19% and DSR of 11-13% [26-28].

In the present study, only a minority of patients was low-grade EOC (13%) and most underwent letrozole. The present patients had a low ORR (2%) and higher DSR (70%) with consequent higher CBR (72%) based on imaging criteria, since the majority of patients were in "maintenance" treatment after chemotherapy and not with progressive disease as the patients in other studies.

Compared to high-grade serous carcinoma, LGSC is characterized by relative chemo-resistance and prolonged survival. Hormonal therapy may be a reasonable choice in the limited number of patients in recurrent setting. A recent robust study of hormonal maintenance therapy *versus* observation after primary treatment in Stages II-IV LGSC concluded that there is a benefit of hormonal maintenance, whether women were disease-free or had persistent disease after the completing platinum-based chemotherapy [22]. In the present study the subset of patients with LGSC had a median PFS of ten months, which is line with a review of 64 LGSC patients, in which time to progression was 7.4 months [18]. However, in general the present patients obtained lower survival rates (PFS 6 and OS 22 months), which might be explained by the small number of LGSC patients (13%) included in the study.

In another phase II study, a greater clinical benefit was shown in patients with higher ER histoscore [29]. Nevertheless, the present study only included a small number of patients in which hormonal receptors were known, which limit conclusions in this field.

Hormonal therapies have a favorable toxicity profile, with a vast experience in breast cancer. Hot flushes is a common side effect with tamoxifen [30]. An increased risk of venous thromboembolism and endometrial cancer are rare adverse events of tamoxifen [31-33]. For aromatase inhibitors, arthralgia/myalgia and loss of mineral density leading to increased risk of fractures have been documented [34, 35]. In the present study no serious adverse advents were reported. However, symptoms related to the advanced disease were commonly mentioned in patient medical records, which may obscure minor toxicity related to the hormonal treatment.

The present authors understand that retrospective nature and heterogeneous population can impair the conclusions in this study. Nevertheless, it has a considerable number of patients. Clinical benefit is superior to the one reported in the literature, probably due to the maintenance use of hormonal therapy in the majority of the present patients.

Conclusion

Hormonal therapy is a low-cost, easily accessible, and overall well-tolerated treatment. The selection of the appropriate patients for this modality of treatment is the main challenge. Although the link of ER and PR overexpression to the efficacy is not yet well-established, hormonal receptors status should be systematically reported in the pathology reports to support clinical decisions. Hormonal maintenance treatment has been proved to increase PFS compared to observation only in LGSC. Prospective studies of hormonal therapy on high-grade serous carcinoma is

desirable mainly for patients unsuitable for other chemotherapeutic options.

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