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Research article

Hormonal Maintenance Therapy versus surveillance in high-Grade Serous Ovarian Carcinoma

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Abstract

Background and objective: In spite of combined treatment modality, the treatment outcomes of ovarian carcinoma is still disappointing. This raises the need to consider maintenance therapy. The object of this study was to assess the results of maintenance hormonal therapy (HMT) in comparison to surveillance after primary cytoreductive surgery and adjuvant platinum-based chemotherapy in women with stage II- IV HGSOC. Patients and methods: This prospective study enrolled 47 women, (1st arm=23 patients, 2nd arm=24 patients) with pathologically proven HGSOC, stage II- IV ,with tumor tissue expressing ER & PR. Patients in the 1st group who were treated by maintenance hormonal therapy (HMT) with tamoxifen 10 mg , given after ending adjuvant chemotherapy, at a dose of 2 tablets daily. The 2nd group included patients who underwent surveillance after completion of adjuvant chemotherapy (control arm). Results: The mean overall survival was 26.5months for patients in the HMT group vs 25 months for those who underwent observation. The 2-year OS was 82% vs 77% in the HMT & surveillance groups, respectively. The mean progression-free survival was 22 months in the HMTarm vs 20 months for those who underwent surveillance (P =0.06). The 2-year PFS was 68.7% vs 49.9% in the HMT & surveillance groups, respectively. Conclusion: Tamoxifen as a HMT in stage II- IV HGSOC after adjuvant chemotherapy, is a tolerable, low cost regimen with easy intake and reasonable activity, expressed as longer PFS in comparison to patients who underwent only surveillance.

Keywords: ovarian serous carcinoma, high grade, maintenance hormonal therapy

Introduction

Advanced ovarian carcinoma is one of the highly lethal gynecological tumors. More than 60% of women present with advanced stage (III–IV) at diagnosis, which is responsible for the high death rate [1]. The gold standard for ovarian carcinoma is cytoreductive surgery, followed by chemotherapy combination of platinum and taxanes, by different regimens [2]. In spite of combined treatment modality, the treatment outcomes of ovarian carcinoma is still disappointing, with a 5 years recurrence rate of 75% for advanced HGSOC [3]. Most of women with HGOSC usually develop disease relapse in spite of expressing clinical response after primary treatment [4].

However, many of relapsed women can be retreated, by several lines of chemotherapy which resulted in a prolonged survival specially over the last decade [2]. This raises the need to consider maintenance treatment, which is one of the strongly recommended options in the treatment of advanced ovarian carcinoma [5]. Maintenance therapy by either chemotherapy or, recently, molecular targeted therapy are considered means of increasing rates of disease control and extending survival without compromising quality of life [6].

However, the cost benefit of new therapies must take into account economical costs beside efficiency and tolerability. So, it is important to have cancer agents not only efficient, but also cost effective [7]. However, ideal chemotherapeutic agents, dosage, treatment interval and duration of maintenance treatment remain unclear and are being investigated [8].

Steroid hormones, mainly estrogen and progesterone are involved in ovarian carcinogenesis. Estrogen is a major regulator of growth and differentiation in ovarian tissue. It is stated that expression of ER and PR may affect tumor behavior and prognosis [9]. Recently, similarity between luminal breast cancer and low grade serous ovarian carcinoma (LGSOC) has been identified. A high percent of low grade serous carcinomas express estrogen (ER) and progesterone receptors (PR), and hormonal treatment achieved clinical response in > 70% of relapses [10].

In a study by Gershenson et al, they examined the results of hormonal maintenance therapy in comparison to observation after primary cytoreductive surgery and platinum-based chemotherapy in patients with stage II - IV LGSC ,the median PFS

was 64.9 months vs 26.4 months in HMT and observation groups ,respectively (P < .001) [11]. A recent trial examined letrozole as maintenance therapy in HGSOC ,which revealed a significant 2year PFS 60% in letrozole group vs 38.5% in the control arm; p = 0.035 [12].

The object of this study was to assess the outcomes of maintenance hormonal therapy (HMT) in comparison to surveillance after primary cytoreductive surgery and adjuvant platinum-based chemotherapy in patients with stage II - IV high grade ovarian serous carcinoma.

Patients and Methods

This prospective study was conducted after acceptance of the Mansoura Faculty of Medicine, institutional research board MFM IRB, at the clinical oncology and nuclear medicine department in collaboration with the pathology department, Mansoura university in the period between January 2016-June 2018 .

Eligibility criteria for this trial were: females patients with pathologically confirmed stage II - IV high grade serous ovarian carcinoma (HGSOC), underwent primary cytoreductive surgery followed by platinum-based chemotherapy, with tumor tissue expressing ER and PR.

Exclusion criteria

Patients with history of thromboembolic events. Pathology slides were reviewed and documented as HGSC of the ovary according to the criteria of FIGO and the World Health Organization (WHO) & immunostaining by CK7, CK20, WT1 and P53. Detection of ER and PR by immunohistochemical staining of tumor tissue was done in the pathology department.

We included 47 eligible patients, who were divided into 2 arms; the 1st (23 patients) who were treated by maintenance hormonal therapy (HMT)with tamoxifen 10 mg , given after ending adjuvant chemotherapy, at a dose of 2 tablets daily. The 2nd (24 patients) included patients who underwent surveillance after completion of adjuvant chemotherapy (control arm). Patients were followed up by clinical examination, abdominopelvic CT or MRI , serum cancer antigen 125. Any side effects of hormonal treatment was graded according to CTCAE, version 4 [13].

Immunohistochemistry

The primary antibodies used were CK7 (DAKO USA clone OV-TL 12/30), CK20 (DAKO USA, clone Ks20.8), WT1 (DAKO USA, clone 6F-H2), P53 (DAKO USA, clone DO-7), ER (DAKO USA, clone 1D5; 1:25) and PR (DAKO USA, clone PgR636; 1:50). Detection kit used high sensitive kit (Dako Cytomation envision +dual link system peroxidase code K4061) using DAB as chromagen. Antigen retrieval obtained by pretreatment with 1 ml mol EDETA (at PH 8.0) for 20 minutes in microwave. Proper positive control for ck20 is normal colon, kidney for WT1, breast tissue for CK7, P53, ER and PR. Negative control was prepared without addition of primary antibody.

Immunohistochemical analysis

The immunohistochemical expression of CK7 and CK20 are membranous staining in the tumor cells while WT1, P53, ER and PR were noted in nuclei of tumor cells. Immunohistochemical results for CK7, CK20 and WT1were evaluated in a semi-quantitative manner and scored; only tumor cells stained in the appropriate membrane/nuclear position were scored. Focal staining was interpreted as positivity in ≤50% of the cells and diffuse staining was interpreted as positivity in >50% of the cells. For statistical analysis cases with any degree of positive staining (focal or diffuse) were considered positive [14]. P53 considered positive if 10% or more of tumor cells were nuclear stained [15]. The ER and PR positivity was defined as ≥ 1% tumor cell nuclei (i.e. encompassing weak, moderate and strong nuclear staining) [16].

Statistical analysis

The statistical analysis was done by SPSS program statistical package for social science version 17. To test the normality of data distribution, K-S (Kolmogorov-Smirnov) test was done, only significant data revealed to be nonparametric. The description of the data done in form of mean (+/-) SD for quantitative data, while frequency & proportion for qualitative data. The analysis of the data was done to test statistical significant difference between groups. For quantitative data, student t-test was used to compare between two groups. Chi square test was used for qualitative data. P is significant if < or = 0.05 at confidence interval 95%. Survival was estimated by Kaplan- Meier survival curve, progression-free survival (PFS) was calculated from date of ending chemotherapy to date of disease progression or death, overall survival (OS) was calculated from date of primary surgery to date of last visit or death.

Table 1. Patients characteristics.

Characteristics	HMT arm N=23	Surveillance arm N=24	P Value
Age (years)			
Median	54	56	0.9
Range	(42 – 64)	(40 – 67)	
ECOG performance status			
0	17(73.9%)	16 (66.7%)	0.8
1	6(26.1%)	8 (33.3%)	
Tumor staging			
II	10(43.5%)	9 (37.5%)	0.6
III	12(52.2%)	13 (54.2%)	
IV	1(4.3%)	2(8.3%)	
Cytoreductive surgery			
optimal	20(86.96%)	21(87.5%)	0.5
suboptimal	3(13.04%)	3(12.5%)	
chemotherapy cycles			
median	6	6	0.9
range	(6-8)	(6-8)	
ER receptors			
+ve	18(78.3%)	-	
-ve	5(21.7%)	-	
PR receptors			
+ve	16(69.6%)		
-ve	7(30.4%)		

Table 2. Tamoxifen-related toxicity.

Toxicities	Hormonal maintenance arm				Surveillance arm				P value
	I	II	III	IV	I	II	III	IV	
Hot flashes	17(73.9%)	0	0	0	16(66.7%)	0	0	0	0.6
Vaginal change*	12(52.2%)	0	0	0	11(45.8%)	0	0	0	0.7
Thromb.*,events	0	0	0	0	0	0	0	0	
Visual comp	0	0	0	0	0	0	0	0	
Hepatic toxicity	0	0	0	0	0	0	0	0	

*Vaginal change (dryness, discharge)

*Thromboembolic

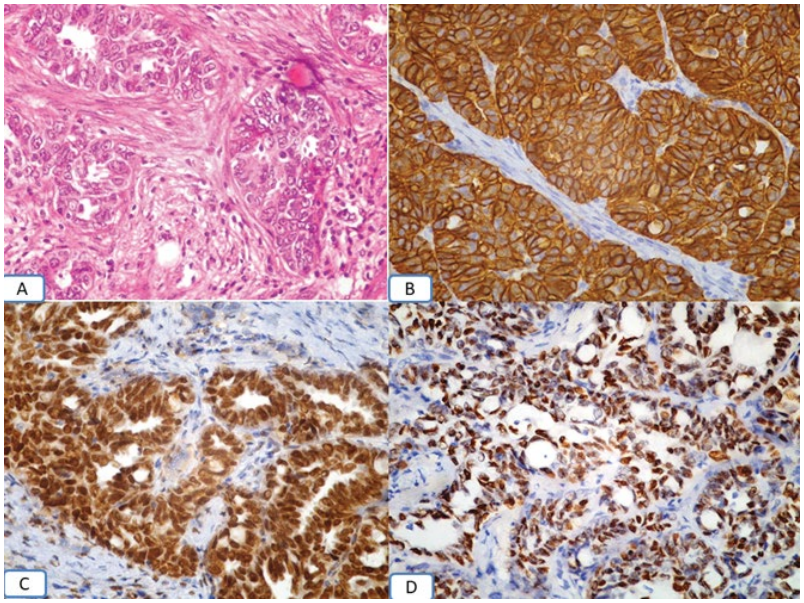

Figure 1. (A)HGSC by hematoxylin-eosin revealed papillary growth with highly pleomorphic and large with coarsely clumped chromatin & psammomma body. (B) Tumor cells show positive membranous staining of CK7. (C) Tumor cells with positive nuclear staining of WT1. (D) Tumor cells with positive nuclear staining of P53 (original magnification x400).

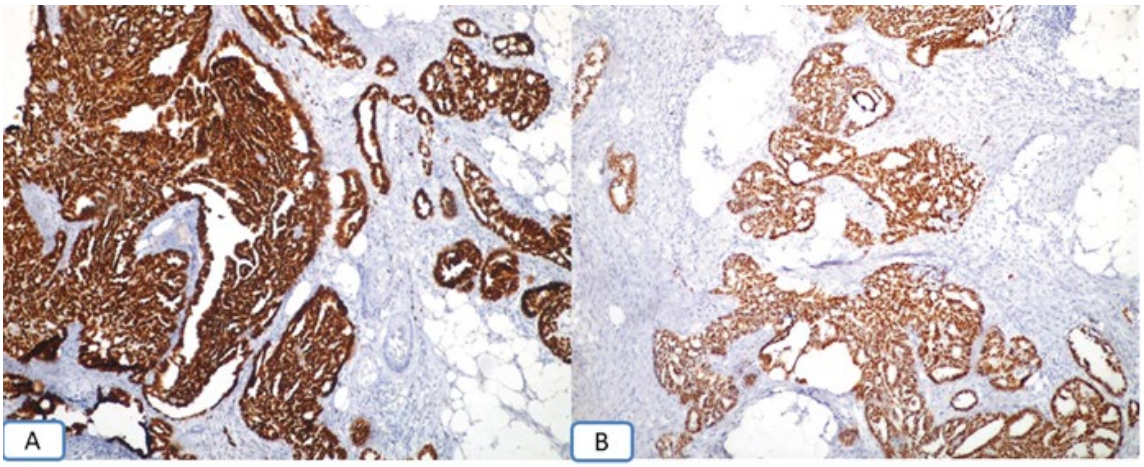

Figure 2. (A) HGSC with positive nuclear staining of ER. (B) Tumor cells with positive nuclear staining of PR (original magnification x100).

Results

We included 47 eligible patients, with pathologically proven HGSOC, stage II- IV, as tumor cells showed positive membranous staining by CK7, negative CK20 and positive nuclear staining by WT1 and P53 (Figure 1), then immunohistochemical staining by ER and PR was done and revealed 24 cases are complete negative for ER and PR; while the remaining 23 cases show 18 cases were ER positive nuclear staining and 16 cases were PR positive nuclear staining (Figure 2).

The patients were then divided into two arms ,(1st arm=23 patients, 2nd arm=24 patients) the first arm; Cases either ER positive or PR positive or combined ER and PR positive, while the second arm is ER and PR negative. Patients' characteristics are comparable between the 2 groups (Table1). All patients in both arms were treated with adjuvant paclitaxel, carboplatin chemotherapy for 6-8 cycles.

The median follow-up was 20 months. The mean OS was 26.5 (95% CI 24.2-28.7) months for patients of HMT arm vs 25 (95% CI 22.6-28.6) months for those who underwent surveillance (P =0.5). The 24months OS was 82% vs 77% in the HMT and surveillance groups, respectively (Figure 3).

The mean PFS was 22 (95% CI 20.5-23.7) months for patients in the HMT arm vs 20 (95% CI 18.4-22.2) months for those who underwent surveillance (P =0.2). The 24months PFS was 68.7% vs 49.9% in the HMT and surveillance groups, respectively (Figure 4).

Regarding toxicity of hormonal treatment, no serious complications was reported by any of the patients, but the commonest side effects detected were hot flashes and vaginal change(discharge, dryness) (Table2).

Discussion

Currently, hormonal treatment with aromatase inhibitors or tamoxifen is only documented in relapsed ovarian carcinoma [17]. Few randomized trials are available and these agents were used to improve PFS [18]. In the present study. The median follow-up was 20 months. The mean OSOS was 26.5months for patients of HMT arm vs 25 months for those who underwent surveillance (P =0.5). The 24months OS was 82% vs 77% in the HMT and surveillance groups, respectively.

Recently, a large retrospective cohort of LGSOC, stage II to IV detected promising results of maintenance hormonal therapy after primary surgery and chemotherapy, 203 eligible patients,133 underwent observation and seventy patients received HMT .The median PFS in the OBS arm was 26.4 months vs 64.9 months in the HMT arm (P < .001), while the OS was comparable between the two groups (102.7 v 115.7 months, respectively) [11].

In a trial examined letrozole as a maintenance therapy in HGSOC. Its use was associated with a significant prolonged PFS (2 year was 60% in letrozole arm vs 38.5% in the control arm; p = 0.035) [12].

A retrospective evaluation of 14 women with advanced ovarian carcinoma with clinically complete response after platinum/taxane chemotherapy ,they were treated with oral etoposide at a dose of 50 mg/day for 21 days per cycle monthly for 3-5 cycles as maintenance chemotherapy. The median PFS was 43.5 months, the median OS was 86 months, and the 5 year OS was 77.1% [4].

Anti-angiogenic agents and PARP-inhibitors are used as 1st and 2nd lines of maintenance treatment .The major drawbacks of these agents is the expensive cost, toxicities and compromized quality of life (QOL) [19]. GOG-218 was a double-blinded phase 3 study enrolled 1873 women with stage III or IV EOC. After surgical cytoreduction, patients were randomly given chemotherapy (CT) alone, CT plus concurrent bevacizumab or CT plus concurrent bevacizumab (15 mg/kg) fol¬lowed by maintenance bevacizumab. The median PFS was 10.3 months in the control group vs11.2 months in the bevacizumab-initiation group, and 14.1 months in the bevacizumab maintenance group [20].

AGO-OVAR 16 is a phase 3 study to assess the efficiency and tolerability of pazopanib vs placebo in patients not progressing after 1st line CT for epithelial ovarian carcinoma. According to the outcomes that were presented in 2013 American Society of Clinical Oncology, maintenance treatment with pazopanib (800 mg/day) increased PFS rates of 900 patients who had completed their first-line treatment (median 17.9 vs 12.3 months, respectively, p=0.0021 [17]. An interim analysis showed no OS improvement. However, an increase of compli-

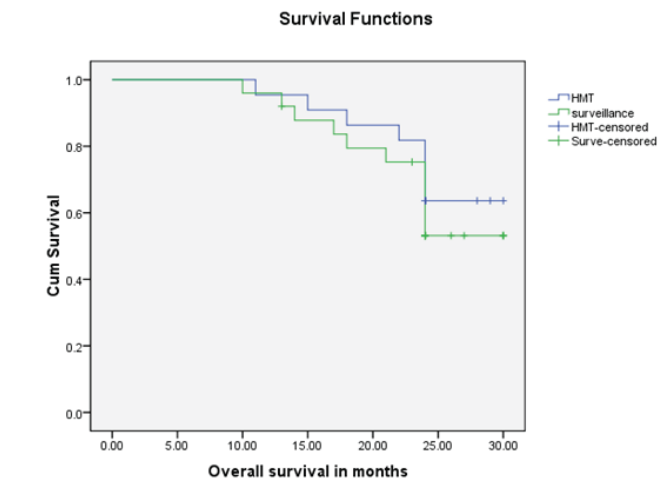

Figure 3. Overall survival.

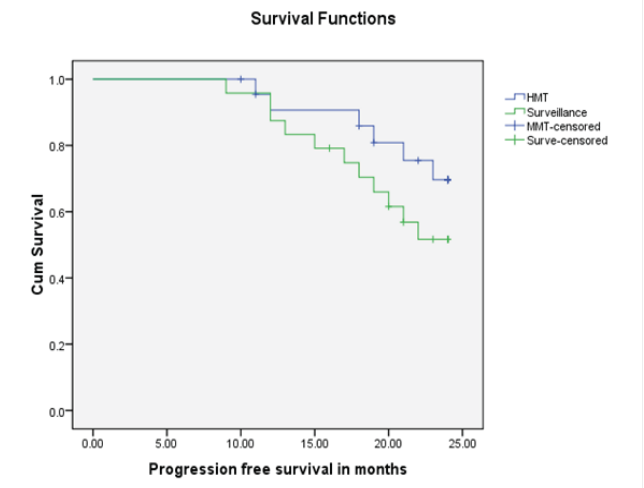

Figure 4. Progression free survival.

cations like grade 2 or greater hypertension (52 vs 17%), grade 3 or 4 diarrhea (8 vs 1%) and grade 3 or 4 hepatotoxicity (9 vs 1%) was observed during pazopanib treatment. Unlike other bevacizumab studies, AGO-OVAR 16 was important for being the first prospective study that evaluated angiogenesis inhibitors as maintenance treatment following fist-line CT [22].

A phase II trial used hormonal treatment for ER +ve relapsed gynecological tumors recorded a response rate of 44% with improvement in QOL in comparison to the control arm [23]. The main limitation of the current study is being non randomized, the limited number of patients and the relative short follow up period.

Conclusion

In summary, ER and PR are considered as prognostic factors and tamoxifen as a maintenance hormonal therapy after primary surgery and adjuvant chemotherapy in stage II - IV HGSOC, is a tolerable, low cost regimen with easy intake and reasonable activity, expressed as a longer PFS in comparison to patients who underwent only surveillance.

Conflicts of Interest: No conflicts of interest

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