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ORIGINAL ARTICLE

The Effect of Hormonal Status on the Results of Aromatase Inhibitor Maintenance Following Adjuvant Chemotherapy for High-Grade Serous Ovarian Cancer (HGSOC)

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ABSTRACT

Background: The prognosis of epithelial ovarian cancer (EOC) depends on the patient's receptor status, which is influenced by hormones. Although there is conflicting evidence about the predictive power of molecular targets such as ER and PgR for tumor response, hormone therapy has the potential to aid patients with advanced EOC.

Objective: The purpose of this study was to analyze the relationship between hormonal status and the success of aromatase inhibitor maintenance after adjuvant chemotherapy for HGSOC.

Method: This study was conducted at the department of Gynae and Obs, DHQ hospital, KDA, Kohat during June 2022 to June 2023. One hundred and ten patients participated in this prospective clinical trial to see how well and safely aromatase inhibitor (AI) maintenance endocrine therapy with 2.5 mg of letrozole daily, given off-label, worked. Patients were treated for a maximum of five years, or until side effects, symptomatic recurrence, or the need for more chemotherapy became apparent. Immunohistochemistry was used to evaluate correlations with ER and PgR. SPSS 22.0 was used to analyze all data.

Results: The included had mean age 53.12 years and had mean BMI 31.54 kg/m^2. Frequency of postmenopausal was higher found in 70 (63.6%) as compared to premenopausal cases 40 (33.6%). Most common symptoms was abdominal pain found in 93 (84.5%) cases. Rate of relapse was found in 46 (41.8%) cases. 26 cases of relapsed disease and 35 cases of non-relapsed received aromatase inhibitorn (AI) maintenance. However, when looking at disease-free survival and relapse rates together, no significant differences were seen.

Conclusion: Our data do not support aromatase inhibitor maintenance therapy for HGSOC. AIs are appealing due to their low cost and safety, but our group's lack of significant improvement in RR or DFS suggests more targeted and customized treatment.

Keywords: HGSOC, aromatase inhibitor, disease free survival, Symptoms

INTRODUCTION

After 5 years, 75% of women with advanced HGSOC will have experienced a recurrence of their ovarian cancer[1-3]. Notwithstanding better treatment options including maximal cytoreductive surgery and new-targeted medicines, the outcome has only marginally improved over the past few decades, especially in HGSOC. This has led to the investigation of several drugs in clinical trials for primary and recurrent ovarian cancer. Medications that inhibit angiogenesis and PARP have demonstrated the greatest potential thus far[4]. Bevacizumab, a VEFG-antibody, was approved for maintenance in a post hoc evaluation for high-risk malignancies[5]. In Europe, patients with germline BRCA mutations or cancers mutated by BRCA can be given the PARP-inhibitor olaparib in the recurrent situation when platinum-based treatment is resumed[6]. Alternatively, olaparib is now approved for use in the United States to treat advanced ovarian cancer in adults who have been through three or more cycles of chemotherapy and have germline BRCA mutations (gBRCAm) that are known or suspected to cause significant side effects [6]. Two other PARP inhibitors, rucaparib and niraparib, have been approved by the FDA since 2016[7].

Therefore, new drugs are critically required to improve outcomes, particularly for these individuals, so they can keep taking their present prescription without degrading their quality of life. One important target that has lately demonstrated new and positive results is anti-hormonal therapy, which is used as a maintenance measure until the next scheduled treatment (TTNT)[8]. Numerous small case series provide evidence that endocrine treatment is beneficial for subgroups of ER+ ovarian cancer patients, particularly those with LGSOC[9]. Gershenson has detailed a retrospective study of 180 individuals' experiences with endocrine maintenance treatment for LGSOC[10]. Patients who were observed alone had a progression-free survival (PFS) of 27.3 months compared to 64.9 months for patients who got endocrine maintenance medication and had platinum-based adjuvant chemotherapy (n=66), with a p-value of less than 0.001. Out of all the patients that were treated, 54% were given letrozole and 28% were given tamoxifen. In 2012, those same authors demonstrated a high rate of clinical improvement in 69 patients treated with 89 distinct hormone treatment regimens for recurrent LGSOC. Patients receiving different endocrine maintenance medication regimens for recurrence had a 9% remission rate and a 62% disease stability rate[11]. Due to the estrogen-pathway's role in ovarian cancer, elevated ER/PR IHC expression is a prognostic indicator that supports the use of endocrine treatments.

Certain subtypes of ovarian cancer can be efficiently treated with hormonal drugs, according to research. These treatments include tamoxifen and letrozole. Indicators for endocrine therapy, such as estrogen receptors (ER) and progesterone receptors (PgR), are still debatable, albeit [12]. Results from a prospective research in HGSOC showed that starting letrozole maintenance medication within three months after adjuvant chemotherapy considerably improved recurrence-free survival (RFS) as compared to observation alone[12]. Regardless of these results, prospective trials investigating endocrine therapy as a maintenance approach in ER/PgR-positive HGSOC are clearly lacking on the subject. We hypothesize that endocrine therapy may be a practical and affordable way to maintain ER/PgR-positive HGSOC, particularly in resource-constrained regions where PARP

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inhibitors and bevacizumab are not readily available. By carrying out this study, we intend to gain a better understanding of how hormone status impacts the efficacy of aromatase inhibitor maintenance therapy following adjuvant chemotherapy in HGSOC.

MATERIALS AND METHODS

Patients with ER/PR positive FIGO stage III/IV HGSOC were compared in this prospective clinical trial to those receiving observation versus maintenance endocrine treatment. The study was conducted at the Department of Gynae and Obs, DHQ hospital, KDA, Kohat during June 2022 to June 2023. After debulking surgery, participants were randomly assigned to receive adjuvant chemotherapy and maintenance aromatase inhibitors (AIs) or no treatment at all. The results were related to the expression of ER and PR as determined by immunohistochemistry. After being informed that they might withdraw from the trial, all participants gave their informed consent, and the ethics committee approved it. Women with FIGO stage III/IV HGSOC, ER/PR-positive status (≥1% nuclear staining on IHC), ECOG performance status ≒2, and a minimum of four platinum-based chemotherapy cycles were included in the study. The participants' ages ranged from 18 to 80. Exclusion criteria included being 80 years old or older, having poor performance, having comorbidities, current illnesses, being pregnant or lactating, using tamoxifen or AI, or having endocrine contraindications.

A thorough medical history, physical examination, and first blood tests (including CEA and CA 125) were administered to all patients. Before beginning aromatase inhibitor (AI) medication and after adjuvant chemotherapy, patients underwent baseline CT scans of the chest, abdomen, and pelvis; further scans were performed as needed. Patients from the cancer and pathology archives at Mansoura University's oncology department had their paraffin blocks examined for pathology. Using rabbit monoclonal primary antibodies (REF 790-4324 for ER and REF 790-2223 for PR), the ROCH automated immunohistochemistry system (VENTANA BenchMark GX) was employed to stain 4 µm tissue slices. When immunohistochemistry revealed faint, moderate, or high staining in tumor cell nuclei (1% or more), it meant that ER and PR were present. The overall score for all ER and PR IHC tests was 300, which was calculated by multiplying the percentage of cells expressing each staining intensity (0 for absent, 3 for high) by the possible maximum score. Patients who tested positive for ER and PgR tumor markers and were recently diagnosed with FIGO stages III and IV HGSOC were randomly allocated to one of two groups. Following adjuvant platinum-based chemotherapy and debulking surgery, 2.5 mg of the aromatase inhibitor (AI) letrozole was administered to one group of patients as a maintenance medication. In the event of severe side effects or symptomatic recurrence, further chemotherapy was delivered during this treatment. Patients had the option to switch to monitoring if they preferred not to undergo maintenance therapy. Participants without AI in the study chose to do nothing more than observe. We only conducted CT and CA 125 scans when we felt it was very necessary from a clinical standpoint. Researchers looked into the potential side effects of AI-assisted anti-hormonal treatment, including bone density reduction. Regular DEXA scans and the use of vitamin D, calcium, or bisphosphonates were components of the breast cancer therapy plan. Here, we'll look at how DFS compares to RR.

If the two-tailed p-value is smaller than 0.05, then there is statistical significance. Quantitative features were characterized by means of percentages, counts of cases, and frequency distributions. In quantitative variable descriptive statistics, the distribution and central tendency were described using the range, median, standard deviation, and mean. The relationships between the category variables were investigated using the Chi-Square Test.

RESULTS

The included had mean age 53.12 years and had mean BMI 31.54 kg/m^2. Frequency of postmenopausal was higher found in 70 (63.6%) as compared to premenopausal cases 40 (33.6%). Most common symptoms was abdominal pain found in 93 (84.5%) cases.(table 1)

Table-1: Demographics of the presented cases

Variables	Frequency (110)	Percentage
Mean age (years)	53.12	
Mean BMI (kg/m^2)	31.54	
Menopausal Status		
Post	70	63.6
Pre	40	36.4
Clinical details		
Abdominal pain	93	84.5
Abdominal enlargement	67	60.9
Bleeding	27	24.5
Urinary symptoms	13	11.8

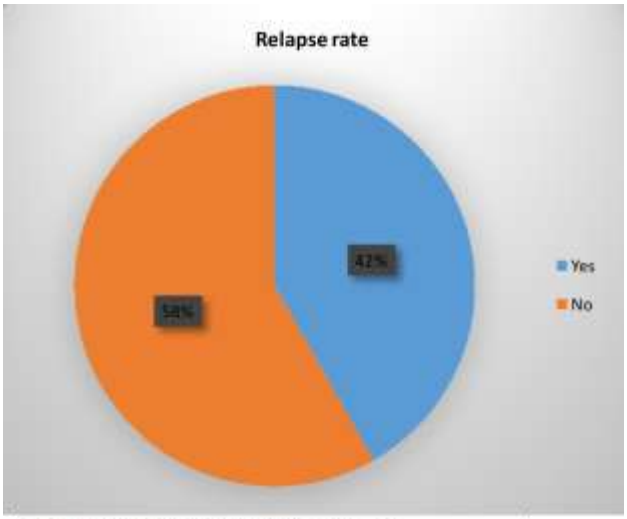

Figure-1: Frequency of relapse among all cases

Rate of relapse was found in 46 (41.8%) cases.(fig 1)

26 cases of relapsed disease and 35 cases of non-relapsed received aromatase inhibitorn (AI) maintenance. However, when looking at disease-free survival and relapse rates together, no significant differences were seen.(table 3)

Table-3: Outcomes among cases after AI maintenance

Variables	Relapsed cases (46)	Non-relapsed (54)
AI maintenance		
Yes	26 (56.5%)	35 (64.8%)
No	20 (43.5%)	19 (35.2%)
Disease free survival		
Yes	13 (23.2%)	11 (20.4%)
No	33 (86.8%)	43 (89.6%)

DISCUSSION

Even though there have been advancements in treatment, the prognosis for ovarian cancer, particularly high-grade serous ovarian carcinoma (HGSOC), is still not very favorable. The outcomes have only marginally improved over the course of the preceding decades, with a recurrence rate of 75% five years after the first diagnosis[13]. Maintenance treatments are an encouraging new strategy by which progression-free survival (PFS) can be extended after the initial treatment has been administered. Anti-angiogenic medicines, such as bevacizumab and PARP inhibitors, are currently considered the gold standard treatment for FIGO stage III-IV HGSOC since they are among the most effective. However, their usage is restricted due to the fact that they are

expensive, highly poisonous, and have a detrimental impact on the quality of life[14-16].

It is common practice to administer aromatase inhibitors (AIs) like letrozole to patients who have hormone receptor-positive breast cancer. Additionally, endocrine therapy has a lengthy history of application in this particular area of study. Despite this, there is ongoing discussion over the possible significance of this component in the treatment of ovarian cancer, particularly with regard to the maintenance treatment. The data that supports the use of endocrine therapy in HGSOC maintenance therapy is limited, although the PARAGON research demonstrated a complete response rate (CBR) of 44% and an improvement in quality of life in estrogen receptor (ER)-positive gynecological malignancies that had relapsed[17,18]. Letrozole was evaluated as a potential maintenance medication for individuals with FIGO stage III-IV HGSOC in a prospective observational trial that was conducted not too long ago.

At 24 months, sixty percent of patients who were treated with letrozole did not experience any recurrences, in contrast to the 38.5% of controls who did not experience any recurrences; this difference was statistically significant ($p = 0.035$)[19]. At the 12-month mark, the recurrence-free rate was significantly higher for letrozole combined with bevacizumab (87.5% versus 20.8%; $p = 0.026$) than it was for bevacizumab alone. Research conducted on breast cancer has demonstrated that artificial intelligences are beneficial and have a minimal risk of adverse effects; hence, these results are consistent with that research[20,21]. On the other hand, our research compared maintenance AI therapy with follow-up for

84 patients with advanced-stage HGSOC. We discovered that there was no statistically significant change in relapse rates (RR) or disease-free survival (DFS) between the two groups of patients. Curiously, a subgroup analysis revealed that patients younger than 50 years old had a lower disease-free survival (DFS) when they were using maintenance AI medication[22] This finding highlights the need for more investigation into this subject. Further highlighting the significance of discovering more precise predictive biomarkers is the fact that there is no association between the presence of hormone receptors (ER/PR positive) and the outcome of treatment.

CONCLUSION

Our data do not support aromatase inhibitor maintenance therapy for HGSOC. AIs are appealing due to their low cost and safety, but our group's lack of significant improvement in RR or DFS suggests more targeted and customized treatment.

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