Original Article

The Role Of Maintenance Hormonal Therapy In High Grade Epithelial Ovarian Cancer

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DOI: 10.47750/pnr.2023.14.02.194

Abstract

Background: Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United State and is the fifth most cause of cancer mortality in women. Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy. Comprehensive surgical staging is the mainstay of diagnosis and initial treatment for ovarian, fallopian tube, and peritoneal cancers. After initial cytoreductive surgery and subsequent chemotherapy, management of EOC may include maintenance therapy. Targeted maintenance therapy is defined as the maintenance administration of a single-agent antibody or small-molecule inhibitor after the completion of chemotherapy. The rationale for maintenance therapy is to delay the disease from progressing by either eliminating residual slowly dying cancerous remnants, retarding cell turnover via inhibitory signaling, preventing tumor neo-angiogenesis, or through immunologic control. Hormonal treatment is commonly used as a treatment option in patients with recurrent ovarian cancer who have exhausted or are not suitable for further standard lines of systemic chemotherapy, also been postulated to be effective in the setting of relapsed disease with a rising CA125 before the onset of significant clinical symptoms. Hormonal therapy provides an attractive therapeutic option in these patients due to the convenience of oral administration, and generally tolerable safety profile compared to chemotherapy and other targeted therapies.

Keywords: hormonal therapy, epithelial ovarian cancer.

INTRODUCTION

Ovarian neoplasms encompass a wide array of benign and malignant tumors with diverse histologic cell types, clinical features, and survival outcomes. Primary malignant tumors are classified based on cell types, patterns of growth and, whenever possible, on histogenesis. **(Kuman, et al 2014)**

The incidence of malignant forms varies with age. Carcinomas, accounting for over 80%, peak at the 6th decade; SCSTs peak in the perimenopausal period; GCTs peak in the first three decades. Prognosis is worse for carcinoma. **(Liao, et al 2018)**

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United State and is the fifth most cause of cancer mortality in women. In 2020 it is estimate that 21,750 new diagnosed and 13,940 deaths from this neoplasm will occur in the United States **(Siegel, et al 2020)**

Because of the location of the ovaries and the biology of the most epithelial cancers, it has been difficult to diagnosis ovarian cancer at the earlier, more curable stage. In the absence of a reliable screening test, most women with ovarian cancer are diagnosed with advanced-stage disease. In contrast to women with localized disease (stage I/II) who have estimated 5-year survival rates of 70% to 90%, overall survival for women with advanced disease (stage III/IV) is poor, ranging from 20% to 45%. **(Smith, et al 2015)**

Diagnostic work up

Evaluation of a pelvic mass will be influenced by the patient's age, clinical presentation, and imaging features. An ovarian mass is more likely to be a malignant neoplasm in the pediatric, perimenopausal, and postmenopausal age groups and benign during the reproductive years. Ultrasound is often the first, noninvasive step for the evaluation of a pelvic mass. **(Kim, et al 2004)** Computed tomography (CT) and magnetic resonance imaging (MRI) may be useful preoperatively for surgical planning to determine the extent of intra- and extra-abdominal disease. An elevated CA-125 level may suggest more advanced or greater bulk of disease and high-grade serous histology but in general is a weak predictor of surgical

resection. (Iyer, et al 2010) FDG-PET/CT scan or MRI may be useful for indeterminate lesions, if they will alter management. **(Yamamoto, et al 2008)**

Primary treatment

Staging and surgical treatment of ovarian cancer

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery , followed in most (but not all) patients by systemic chemotherapy. Comprehensive surgical staging is the mainstay of diagnosis and initial treatment for ovarian, fallopian tube, and peritoneal cancers. In patients with advanced disease, patient with clinical stage II,III or IV disease surgery represents the initial treatment by providing optimal Surgical debulking is optimal if the residual tumor nodules are less than 1cm in maximal diameter or thikness. (**Fader, et al 2007)** The goal is resection R0. Extensive resection of upper abdominal metastasis is recommended for patient who can tolerate this surgery. A maximal effort should be made to remove all gross disease, because the more complete the debulking the better outcome. **(Fader, et al 2007)**

When thorough assessment of tumor spread and performance status of the patient indicates that complete primary cytoreduction is not feasible without unacceptable morbidity, then alternative therapeutic strategies, such as neoadjuvant chemotherapy (NACT) must be considered. These patients can be offered IDS after response to NACT and resolution of the initial obstacles for PDS (ie, complete response of irresectable disease, improvement of the performance status). **(Chi, et al 2009)**

Adjuvant chemotherapy for advanced stage epithelial ovarian cancer

The majority of women with EOC present with stage II or IV disease. All patients with EOC, even those with stage IV disease, have an improved prognosis with optimal cytoreductive surgery. The standard of care for the treatment of advanced stage EOC is maximal cytoreductive surgery followed by at least six cycles of a platinum/taxane combination regimen. **(Cristea, et al 2010)**

Maintenance Therapy

After initial cytoreductive surgery and subsequent chemotherapy, management of EOC may include maintenance therapy. With maintenance therapy, women who achieve a response to initial adjuvant chemotherapy go on to receive additional therapy with the goal of inducing a lasting remission, or prolonging the disease-free interval before recurrence therapy should demonstrate a favorable side-effect profile and have minimal negative effects upon QoL. The rationale for maintenance therapy is to delay the disease from progressing by either eliminating residual slowly-dying cancerous remnants, retarding cell turnover via inhibitory signaling, preventing tumor neo-angiogenesis, or through immunologic control. **(Khalique, et al 2014)**

Targeted maintenance therapy is defined as the maintenance administration of a single-agent antibody or small-molecule inhibitor after the completion of chemotherapy. Currently, the two most commonly and successfully employed maintenance strategies include antiangiogenic therapies and PARP inhibitors**. (Ray-Coquard, et al 2019)**

Therapies that target tumor vasculature, such as antiangiogenic agents, have therefore made their way into the EOC armamentarium. Currently, only one antiangiogenic therapy, bevacizumab, is approved for treatment of EOC**. (Hall, et al 2013)** Bevacizumab, is indicated for the treatment of patients with recurrent EOC in the US and for both newly diagnosed and recurrent EOC in Europe. Bevacizumab combined with paclitaxel, pegylated liposomal doxorubicin, or topotecan is approved for women with platinum-resistant recurrent EOC who received no more than two prior chemotherapy regimens. **(Ray-Coquard et al 2019)**

Results from the phase III GOG-0218 and ICON7 trials support the use of the single-agent bevacizumab maintenance therapy for patients with stage II-IV disease who experience response or stable disease after postoperative chemotherapy with one of the carboplatin/paclitaxel/bevacizumab regimens used in these trials. **(Ray-Coquard et al 2019)** Based on these results bevacizumab monotherapy was a recommended option for maintenance for patients with stage II-IV disease who were in CR/PR after a primary treatment with surgery and one of the bevacizumab –containing regimens recommended in the first-line setting. **(Ray-Coquard et al 2019)**

PARP inhibitors approved for maintenance therapy

Three PARP inhibitors are approved for maintenance therapy in patients with EOC based on several phase III double-blind, randomized trials tested PARP inhibitors as maintenance therapy for patients with newly diagnosed , stage III-IV ovarian cancer who have complete first-line chemotherapy. On May 8, 2020, the FDA expanded olaparib's indication to include the combination with bevacizumab for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary

peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic stability. **(FDA approval 2020)** Rucaparib has been recently approved by the FDA as monotherapy for the treatment of ROC patients who are carriers of deleterious (germline and/or somatic) BRCA mutations. **(Syed, et al 2017)**
On April 29, 2020, the FDA approved niraparib for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. **(FDA –approval 2020)**

The role of Hormonal theray in ovarian cancer
Hormonal treatment is commonly used as a treatment option in patients with recurrent ovarian cancer who have exhausted or are not suitable for further standard lines of systemic chemotherapy, also been postulated to be effective in the setting of relapsed disease with a rising CA125 before the onset of significant clinical symptoms. (**Zheng et al 2007)**

Hormonal therapy provides an attractive therapeutic option in these patients due to the convenience of oral administration, and generally tolerable safety profile compared to chemotherapy and other targeted therapies. Although there is a strong evidence base to support the use of hormonal therapy in the treatment of early and metastatic estrogen receptor ER-positive breast cancer, there are few prospective clinical trials evaluating this approach in recurrent ovarian cancer. **(Gershenson et al 2012)** The rate of ER-positivity in epithelial ovarian cancer is reported to be 43–81%, depending on the definition and methodology used. Pre-clinical models have demonstrated that ovarian cancer cells that express high levels of estrogen receptors are stimulated by estrogens and inhibited by anti-estrogens, providing rationale for the use of hormonal therapy in this disease. **(Escobar et al 2013)**
Estrogen signaling in OC

ER is highly expressed in several EOCs and is a potential target for endocrine therapy. Studies using in vitro experiments and in vivo animal models of EOC support the hypothesis that ER expression levels are a crucial determinant of the response to treatment with selective ER modulators. In addition, epidemiological studies have demonstrated that the long-term use of estrogen-only therapy increases the risk of developing OC in women, supporting the hypothesis that estrogen signaling contributes to the etiology of the disease. (**Hoffmann, et al 2019)**

In vitro cultured EOC cells exhibiting a high ERα expression can be stimulated by estrogen, while treatment with selective ER modulators (tamoxifen and fulvestrant) can inhibit the growth of EOC cell xenografts with a high ERα expression in vivo. By contrast, estrogen has been shown to exert no effect on ERα-negative cell lines. **(Liu, et al 2014)**

Consistent with its tumor-suppressive effect, the high expression of ERβ1 in the cytoplasm of EOC cells has been found to be strongly associated with a longer disease-free and overall survival of patients. In contrast to the inhibitory role of ERβ1, both ERβ2 and ERβ5 have been associated with pro-migratory and invasive activities. ERβ2 overexpression has been shown to increase cell migration and invasion, but not the proliferation of EOC cells. **(Chan, et al 2017)**

Tamoxifen was the first selective ER modulator to be evaluated in clinical trials for OC and is still in use today; it is considered to function as a selective ER modulator that competes with estrogen for binding to the ERα and, thus, functions as an ER antagonist. The majority of studies were designed as single-arm studies to assess whether tamoxifen can induce a response in EOC; however, they did not evaluate the effects of tamoxifen on symptom control, the quality of life or the survival time of patients. It has been reported that the overall mean response rate of this treatment is 10–15%, and the disease stability rate is 30–40%. (**Paleari, et al 2017)** In clinical trials in which tamoxifen was applied, the majority of patients had undergone major pre-treatment procedures, such as chemotherapy, and several studies did not differentiate between ER-positive patients. Perez-Gracia and Carrasco, reported an overall response rate of 26% and a complete response rate of 9% in the analysis of trials using tamoxifen in at least 50% of cases not having received multiple prior treatments, compared with a clinical study treating patients with severe disease with an effectiveness rate of only 4%. **(Perez-Gracia, et al 2002)**

For 19 years, non-steroidal aromatase inhibitors have been studied for their antitumor activity, which appears to be comparable to that of tamoxifen, by inhibiting the conversion of androgens to estrogens, thereby reducing circulating estrogen levels. Paleari et al 2017 reviewed 53 endocrine therapy trials including a total of 2,490 patients in their meta-analysis. The clinical benefit rate (CBR; percentage of total patients exhibiting complete response, partial response or SD in all endocrine therapy evaluations) reached 41%; the CBR for tamoxifen was 43% (23 trials) and the CBR for aromatase inhibitors was 39%

(10 trials), demonstrating that the effectiveness of the two types of drugs was comparable for patients with advanced EOC. **(Paleari et al 2017)**

According to a recently conducted trial (PARAGON), the application of anastrozole in a phase II study on asymptomatic cases suffering from ER- and PR-positive recurrent EOC with CA125 progression was assessed. The response rate reached 4%, and the CBR reached 35%, which was disappointing, given that these cases only had limited disease and had previously received single chemotherapy treatment. (**Kok, et al 2019)**

Two recent reports described studies evaluating the use of endocrine therapy at their respective centers and provided insight into settings outside of HGSOC trials. An analysis of 97 patients treated at the Royal Marsden Hospital (London, UK) investigated the use of tamoxifen and letrozole for advanced EOC (91% HGSOC). (**George, et al 2017)**

More than a quarter of the patients had previously received five or more types of chemotherapy, and half of these had an unknown ER status, whereas the CBR reached 60% (tamoxifen, 65%; and letrozole, 56%). Cases responding to letrozole had a significantly longer response time. **(George, et al 2017)**

A 25-year analysis of 269 cases with HGSOC in Edinburgh revealed a comparable overall response rate for letrozole and tamoxifen (8 and 11%, respectively) and CBR (41 and 33%, respectively). Cases with a high ER expression and a longer treatment-free interval were most likely to benefit from these treatments. **(Stanley, et al 2019)**

The conclusions of these two analyses are consistent with the findings of clinical trials, demonstrating that tamoxifen or letrozole constitute reasonable treatment options for patients with ER-positive HGSOC, with a comparable overall response rate, CBR and disease stability. Endocrine therapy may be a promising alternative therapy for LGSOC, which is less sensitive to chemotherapy. Gershenson et al 2017, identified a 9% response rate and 61% disease stabilization rate in a retrospective analysis of 64 LGSOC cases who had received a total of 89 hormonal regimens. The PFS for cases receiving hormonal maintenance therapy (primarily letrozole or tamoxifen) was 65 months, compared with 26 months for cases under observation only (P<0.001). **(Gershenson, et al 2017)**

That study was followed-up by Fader et al 2017, who also retrospectively explored the use of adjuvant hormonal therapy following surgery without chemotherapy, with promising results. (**Fader et al 2017)**

A phase III trial initiated in 2019 (NRG-GY019) is also currently ongoing. Specifically, the comparison is between paclitaxel/carboplatin + letrozole vs. letrozole independently for stage II–IV LGSOC. **(Slomovitz, et al 2020)** To date, there is limited information available on the sensitivity of endometrioid OC to hormone therapy. In the Royal Marsden High Grade Ovarian Cancer Study, a total of 5 patients with high-grade endometrioid OC were treated with endocrine therapy and, encouragingly, 3 patients exhibited partial remission, while the remaining 2 patients had SD . (**George et al 2017)**

In a study on letrozole reported by Bowman et al 2002, 4/11 endometrioid OC cases had SD compared with 4/43 serous carcinoma cases. Moreover, estrogen-targeting therapies have exhibited considerable promise in the treatment of GCTs. **(Bowman, et al 2002)**

Interesting data of hormonal therapy have also been reported in LGSOC, during the 2016 ASCO annual meeting. A long-term retrospective study of 204 patients with FIGO stage II-IV low grade serous carcinoma demonstrated that hormonal therapy given as maintenance following primary treatment reduced the risk of disease progression by 77%, compared with surveillance ($p < 0.001$). **(Gershenson et al 2017)**

Hormonal maintenance therapy was associated with a statistically significant increase of the median PFS (64.9 versus 27.3 months; hr ¼ 0.23; $p < 0.001$) compared with the surveillance; this benefit seems to be greater in patients without evidence of disease after chemotherapy (median PFS 81.1 versus 29.9 months $p < 0.001$) and gained also a prolongation of median overall survival (191.3 versus 106.8 months; p ¼ 0.04). (Gershenson et al 2017)

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