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REVIEW PAPER

Neoadjuvant chemotherapy in advanced-stage ovarian cancer – state of the art

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Abstract

Ovarian cancer represents the fifth cause of cancer death among women, carrying one of the worst prognoses among gynaecological malignancies. The need to achieve no residual disease after surgery in order to optimize prognosis of advanced-stage ovarian cancer introduced the idea of neoadjuvant chemotherapy. The present review aims to summarize current state-of-the-art evidence regarding the efficacy and safety of neoadjuvant chemotherapy as well as novel insights regarding the usage of modern therapeutic regimens in the context of neoadjuvant chemotherapy. The last decade has been characterized by the breakthrough scientific evidence that neoadjuvant chemotherapy followed by interval debulking surgery for advanced-stage ovarian cancer may be comparable to primary debulking surgery. Neoadjuvant chemotherapy followed by interval debulking surgery is an acceptable – if not preferable – therapeutic approach in advanced-staged ovarian cancer patients because it is associated with higher optimal debulking surgery, fewer complications, and non-inferior survival outcomes. The addition of bevacizumab to chemotherapy contributes significantly to survival outcomes without causing side effects that outbalance the benefits. Patients with recurrent high-grade serous ovarian cancer and a germline or breast cancer mutation should be offered maintenance olaparib after a response to platinum-based chemotherapy. Finally, the role of hyperthermic intraperitoneal chemotherapy in the context of neoadjuvant chemotherapy remains unjustified.

Key words: neoadjuvant chemotherapy, ovarian cancer, PARP inhibitors, diagnostic laparoscopy, state of the art.

Introduction

Ovarian cancer represents the fifth cause of cancer death among women, carrying one of the worst prognoses among gynaecological malignancies [1]. Standard methods of treatment for advanced-stage ovarian cancer enrol both cytoreduction surgery, also called optimal debulking, as well as platinum-based chemotherapy [2]. The need to achieve no residual disease after surgery in order to optimize the prognosis of advanced-stage ovarian cancer introduced the idea of neoadjuvant chemotherapy followed by interval debulking surgery in an effort to reduce tumoural size in the case of non-operable advanced-staged ovarian cancer patients. It is now evident that the strategy of neoadjuvant chemotherapy for stage IIIC and more has led to a significant positive impact among ovarian cancer patients. However, because research is still leading to significant innovations, further amelioration of neoadjuvant chemotherapy by the addition of novel regimens such as anti-VEGF antibodies may also be achieved.

The present review aims to summarize state-of-the-art evidence regarding the efficacy and safety of neoadjuvant chemotherapy as well as novel insights regarding the use of modern therapeutic regimens in the context of neoadjuvant chemotherapy.

Neoadjuvant chemotherapy and interval debulking vs. primary debulking surgery

The last decade has been characterized by the breakthrough scientific evidence that neoadjuvant chemotherapy followed by interval debulking surgery for advanced-stage ovarian cancer may be comparable to primary debulking surgery.

There have been 3 major randomized controlled trials (RCTs) that indicated the effectiveness of neoadjuvant chemotherapy [3–5]. The first of them was

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the study published by Vergote *et al.* in 2010. In this study, the authors randomly assigned 670 patients with stage IIIC or IV ovarian cancer [4]. They observed that largest residual tumour was 1 cm or less in diameter in 80.6% of patients after interval debulking vs. 41.6% in primary debulking. Also, postoperative rates of adverse effects and mortality tended to be higher after primary debulking, while hazard ratios for death and progressive disease were comparable within the study groups. The authors concluded that neoadjuvant chemotherapy followed by interval debulking was not inferior to primary debulking surgery followed by chemotherapy, while complete resection was achieved in a significantly higher pattern in patients treated with neoadjuvant chemotherapy. The therapeutic schema of neoadjuvant chemotherapy consisted of 3 courses of chemotherapy initiated 3 weeks after biopsy. Each course was given every 3 weeks and consisted of cisplatin (starting dose of at least 75 mg/m^2 per 3 weeks, or other schedules containing a minimum of 25 mg/m^2 per week) or carboplatin-containing regimen (dose of AUC 5 based on ethylenediamine tetra-acetic acid or iohexol determination).

The results of the aforementioned study were further confirmed by 2 consequent RCTs that were published in 2011 and 2015 [4, 5]. Kehoe *et al.* [5] published a multicentre RCT in which they enrolled 552 women. They also demonstrated that median overall survival was comparable between the study groups, namely 22.6 months in the primary-surgery group vs. 24.1 months in the primary chemotherapy group. The HR for death was 0.87 in favour of primary chemotherapy, with the upper bound of the one-sided 90% CI being 0.98 (95% CI: 0.72–1.05) [5] . Grade 3 or 4 postoperative adverse events and deaths within 28 months of surgery were more common in the primary-surgery group than in the primary-chemotherapy group (24% vs. 14%, $p = 0.0007$ and 6% vs. < 1%, $p = 0.001$, respectively). Therefore, the authors also concluded that in women with stage III or IV ovarian cancer, survival with primary chemotherapy is non-inferior to primary surgery. As a result, in this study population, giving primary chemotherapy before surgery is an acceptable standard of care for women with advanced ovarian cancer.

Regarding the therapeutic schema, each 3-week chemotherapy cycle consisted of carboplatin AUC 5 or AUC 6 plus paclitaxel 175 mg/m^2 or an alternative carboplatin combination regimen, or carboplatin monotherapy.

It is evident, therefore, that neoadjuvant chemotherapy followed by interval debulking surgery is an acceptable – if not preferable – therapeutic approach in advanced-staged ovarian cancer patients because it is associated with higher optimal debulking surgery, fewer complications, and non-inferior survival outcomes. The optimal therapeutic schema remains the 3-week-based one, in which regimens are administered once every 3 weeks and not on weekly basis as stated in the European Society of Medical Oncology and European Society of Gynaecological Oncology (ESMO-ESGO) 2018 ovarian cancer guidelines [6]. Therefore, 3-weekly carboplatin/paclitaxel remains the standard-of-care chemotherapy of first-line ovarian cancer treatment.

Selection of patients for neoadjuvant chemotherapy

The issue of potentially highest importance is that of appropriate selection of patients for primary debulking or neoadjuvant chemotherapy. According to ESMO-ESGO 2018 ovarian cancer guidelines [6], the selection of patients must be carried out in a specialist ovarian cancer centre. It is also important to emphasize the critical role of complete tumour resection at upfront debulking. ESMO-ESGO clearly define that patients with the following are not appropriate for primary debulking surgery:

- diffuse deep infiltration of the root of small bowel mesentery;
- diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to short bowel syndrome (remaining bowel < 1.5);
- diffuse involvement/deep infiltration of:
  – stomach/duodenum,
  – head or middle part of the pancreas;
- involvement of the coeliac trunk, hepatic arteries, or left gastric artery;
- central or multisegmental parenchymal liver metastases;
- multiple parenchymal lung metastases (preferably histologically proven);
- non-resectable lymph nodes;
- brain metastases.

To conclude, it seems that both options (primary or interval surgery) are acceptable and equal. However, if the decision is made to perform primary surgery, optimal debulking must be achieved to optimize the prognosis. In this context, consideration of current guidelines may contribute to proper patient selection.

The addition of bevacizumab to neoadjuvant chemotherapy

Bevacizumab is an anti-VEGF antibody that has demonstrated significant anticancer activity in advances-stage ovarian cancer [7]. There have been several RCTs performed regarding the comparative effectiveness of chemotherapy with bevacizumab vs. without, the majority of which (GOG2018, OCEANS, AURELIA, GOG 2013) [8–11] indicated a significantly higher progression-free survival in patients treated with the addition

of this antibody. Only the ICON7 [12] trial initially indicated no superior survival outcomes, while a later exploratory analysis of the same study presented some survival benefit in high-risk patients.

A recent systematic review and meta-analysis published in 2017 by Wu *et al.* confirmed the aforementioned results [13]. The authors performed a meta-analysis of 5 RCTs [8–12] including 4994 patients and showed that the addition of bevacizumab in high-risk for progression patients significantly improved progression-free survival (hazard ratio 0.76, 95% CI: 0.68–0.84) and overall survival (hazard ratio 0.85, 95% CI: 0.74–0.96). Furthermore, they noted that also in recurrent ovarian cancer, the addition of bevacizumab to chemotherapy significantly extended progression-free survival, demonstrating a remarkable hazard ratio of 0.53 (95% CI: 0.45–0.63), as well as overall survival (HR 0.87, 95% CI: 0.77–0.99).

Regarding side-effects, bevacizumab is associated with increased risk for hypertension, proteinuria, and bleeding, while the great issue regarding the optimal usage and placement in the totality of the therapeutic approach remains the 2.8-fold increase of gastrointestinal perforations that it causes. However, it is evident that the addition of bevacizumab to chemotherapy provides significant benefits that outbalance the potential side effects.

The aforementioned results regarding the contributory effect of bevacizumab to survival outcomes triggered oncologists to examine its potential usage in the context of neoadjuvant chemotherapy as well. The efficacy and safety of bevacizumab-containing neoadjuvant chemotherapy followed by interval debulking surgery in advanced-stage ovarian cancer was tested by the French ANTHALYA trial [14]. This was a multicentre, open-label, non-comparative phase-II study that randomized patients 2:1 to receive 4 cycles of neoadjuvant carboplatin-Taxol chemotherapy with or without three cycles of bevacizumab 15 mg/kg. Carboplatin was administered at AUC 5 mg/ml/min and paclitaxel at 175 mg/m^2 in a 3-week-based therapeutic schema.

The authors concluded that the rate of optimal cytoreduction was higher than the anticipated rate. Indeed, the complete resection rate was at 58.6% of overall patients, which was already above the statistically pre-defined limit of 45%, while the relative rate in the no-bevacizumab group was only 51.4%. The rate of grade ≥3 adverse events was comparable in both groups (62% vs. 63%), while the rate of postoperative complications was higher in the non-bevacizumab group (36% vs. 28%, respectively). In conclusion, authors stated that the primary objective of safety was achieved because the complete resection rate was significantly higher than the reference rate, and bevacizumab may be safely added to a preoperative program in patients deemed non-optimally resectable. However, their exact role in the setting should be further investigated.

To summarize, it is evident that the addition of bevacizumab to chemotherapy contributes significantly to survival outcomes without causing side effects that outbalance the benefits. It has recently been proven that the addition of bevacizumab may be feasible and safe in the setting of neoadjuvant chemotherapy. Therefore, as recommended by ESMO-EGSO 2018 ovarian cancer guidelines [6], bevacizumab can be safely administered in the neoadjuvant setting before and after interval debulking surgery (IDS) if the interval between surgery and administration is at least 4–6 weeks. However, further research should be performed to specify the exact sub-group of patients that may benefit most from its addition.

PARP inhibitors and neoadjuvant chemotherapy

Poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) have recently been outraised as maintenance therapy both for patients with newly diagnosed, high-grade serous ovarian cancer and breast cancer (BRCA) half mutation, as well as in patients with platinum-sensitive, relapsed ovarian cancer and BRCA half mutation [15–17]. Specifically, regarding newly diagnosed cases, the SOLO1 study, a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial, indicated that median progression-free survival with olaparib was significantly higher in the olaparib group compared with controls [15]. Also, regarding relapsed cases, Pujade-Lauraine *et al.* recently published an international multicentre, double-blind, randomized, placebo-controlled, phase-3 trial enrolling patients with platinum-sensitive, relapsed ovarian cancer [17]. The authors clearly demonstrated that median progression-free survival was significantly longer with olaparib (19.1 months) than with placebo (5.5 months), with the estimated hazard ratio being 0.30 (95% CI: 0.22–0.41). Furthermore, no detrimental effect on quality of life was indicated in patients treated with olaparib. Therefore, as also stated by recent ESMO guidelines, patients with primary and recurrent high-grade serous ovarian cancer and a germline or tumour BRCA mutation should be offered maintenance olaparib treatment after chemotherapy.

However, when focusing on neoadjuvant chemotherapy, there has been no RCT performed to justify the use of PARP inhibitors in the overall neoadjuvant setting. It is of great interest to examine the potential beneficial impact of PARP inhibitors in addition to classic neoadjuvant chemotherapy, preferably in the subgroup of BRCA mutated patients. Meanwhile, the use of PARP inhibitors may be rather restricted to platinum-sensitive, BRCA-mutated patients.

Hyperthermic intraperitoneal chemotherapy in ovarian cancer

The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery has been studied only by a single multicentre, open-label, phase-3 trial. Van Driel *et al.* [18] randomly assigned 245 patients who had at least stable disease after 3 cycles of carboplatin (area under the curve 5–6 mg/ml/min) and paclitaxel (175 mg/m^2 body surface area) to undergo interval cytoreductive surgery either with or without administration of HIPEC with cisplatin (100 mg/m^2). In their intention-to-treat analysis, disease recurrence or death occurred in 89% of patients without HIPEC vs. 81% of patients with HIPEC, which demonstrated a statistically significant difference. Median recurrence-free survival was 10.7 months in the surgery group vs. 14.2 in the surgery plus HIPEC group . Furthermore, the rate of patients presenting grade 3 or 4 adverse events was similar in the 2 groups.

As a result, the authors concluded that among patients with stage III epithelial ovarian cancer, the addition of HIPEC may be beneficial regarding recurrence-free and overall survival of patients, compared to surgery alone. This is currently the only published level-I evidence regarding the role of HIPEC in the neoadjuvant setting. However, as reported in recent ESMO-ESGO guidelines, HIPEC should not be considered a standard of care in first-line treatment. Furthermore, there is still no high-quality evidence of whether the HIPEC strategy is superior to a strategy including the addition of bevacizumab to standard chemotherapy treatment.

Conclusions

Neo-adjuvant chemotherapy is a safe and effective alternative for inoperable patients with advanced-stage ovarian cancer. It represents a therapeutic approach regarding oncological outcomes comparable with the primary debulking approach. Appropriate selection of patients is extremely important to optimize therapy; therefore, non-operability criteria should be strictly followed. A 3-weekly schema with carboplatin/Taxol remains the gold standard therapeutic regimen. The addition of bevacizumab to the neoadjuvant setting is recommended before and after IDS. The use of PARP inhibitors in the neoadjuvant setting has not been studied. Finally, HIPEC may be beneficial in advanced-stage ovarian cancer patients; however, it does not represent first-line treatment according to current evidence.

Disclosure

The authors report no conflict of interest.

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