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Review

Current Status and Controversies in Neoadjuvant Chemotherapy for Advanced Stage Ovarian Cancer: A Review

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Abstract

Objective: To evaluate the role of neoadjuvant chemotherapy (NACT) in the management of advanced ovarian cancer (AOC), with a focus on patient eligibility, pre-NACT diagnosis, treatment, timing of interval cytoreductive surgery (ICS) and the target of ICS, challenges in ICS, response assessment, changes in the tumor microenvironment during NACT, platinum resistance. **Mechanism**: NACT precedes cytoreductive surgery and shrinks tumors, thereby improving surgical success. **Findings in Brief**: NACT shows promising results for improving tumor reduction rates and improve prognosis. **Conclusions**: NACT has emerged as a promising treatment strategy for AOC.

Keywords: advanced stage ovarian cancer; neoadjuvant chemotherapy; interval cytoreductive surgery

1. Introduction

Epithelial ovarian cancer (EOC) is the most prevalent type of ovarian cancer and the ninth most commonly diagnosed cancer type in women globally [1]. Unfortunately, due to the absence of specific clinical symptoms and effective screening, ovarian cancer is generally diagnosed at an advanced stage, leading to poor survival outcomes [2]. Despite radical surgery for advanced ovarian cancer (AOC), microscopic disease may still persist, thus making survival heavily reliant on chemosensitivity [3].

In a landmark retrospective study published in 1975 [4], Griffiths demonstrated a significant correlation between post-surgery residual tumor size and patient survival, leading to the adoption of primary cytoreductive surgery (PCS) followed by platinum-based chemotherapy as the conventional treatment for advanced stage EOC patients. The aim of tumor cell reduction is to reduce the tumor tissue mass as much as possible. A maximum residual tumor diameter of not more than 1 cm is the benchmark for satisfactory tumor cell reduction in order to improve prognosis. However, PCS may not be suitable for elderly patients, patients in which it is difficult to achieve satisfactory tumor reduction, and patients with complications such as hypertension and diabetes who may not be able to undergo major surgery.

An alternative treatment strategy employing neoadjuvant chemotherapy (NACT) combined with interval cytoreductive surgery (ICS) has been introduced to treat AOC that cannot be completely resected. NACT can reduce the size and extent of tumors, decrease surgical complexity and complications, and increase the likelihood of satisfactory tumor reduction, thereby improving the prognosis of AOC patients [3]. Despite its potential benefits, NACT remains the subject of considerable debate and controversy.

This article reviews the current status of NACT in the treatment of AOC. We aim to provide insights for investigators and clinicians that will lead to further cooperative research and clinical intervention.

2. Patient Eligibility Criteria for NACT

NACT is primarily recommended for high-grade serous or endometrioid EOC. Vergote *et al*. [5] suggested the following criteria as suitable for NACT: patients with abdominal metastases, including involvement of the superior mesenteric artery; diffuse deep infiltration into the radix mesenterii of the small intestine; diffuse and confluent stomach and/or small intestine carcinomatosis affecting such extensive areas that resection would result in a short bowel syndrome or a total gastrectomy; multiple parenchymatous liver metastases in both lobes; intrahepatic metastases; tumor-infiltration of the duodenum and/or pancreas and/or the large vessels of the hepatoduodenal ligament; celiac axis or behind the porta hepatis. NACT is also indicated for patients with extra-abdominal metastases that cannot be completely resected, such as multiple pulmonary parenchymal metastases, lymph node metastases and brain metastases. Additionally, NACT is appropriate for patients with reduced performance status and co-morbidity factors that do not allow a “maximal surgical effort” to achieve complete removal. Lastly, NACT is considered for patients who do not accept potential supportive interventions such as blood transfusions or temporary stoma.

However, there is no widely accepted criteria for NACT, with further studies needed to define more applicable criteria.

3. Diagnosis before NACT

Accurate diagnosis of ovarian cancer must be made before NACT. At present, the commonly used auxiliary diagnosis methods include: tumor markers such as cancer antigen 125 (CA-125), human epididymis protein 4 (HE4) and the risk of ovarian malignancy algorithm (ROMA) index; imaging methods such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography–computed tomography (PET-CT); cytology and histology examination.

Conducting simultaneous tumor marker tests helps narrow down the potential diagnoses during evaluation, especially when cytology alone is used to identify the primary condition.

CT continues to be the primary step in the diagnostic process for ovarian cancer. However, CT shows unsatisfactory diagnostic accuracy in detecting malignant abdominal lymph nodes and the presence of peritoneal metastases, thereby resulting in inaccuracy in predicting a (sub)optimal cytoreduction [6]. CT findings should be approached with caution when making decisions between PCS and NACT. A recent meta-analysis revealed that MRI exhibited a sensitivity of 91% and specificity of 85% in diagnosing ovarian cancer [7], which means MRI surpasses CT and PET-CT in detecting ovarian cancer. Multiple studies have shown that diffusion-weighted imaging (DWI)-MRI is dependable for visualizing and quantifying peritoneal metastases using the peritoneal cancer index [8,9]. This suggests that MRI could establish itself as the primary imaging method for AOC, aiding in the selection of patients eligible for complete cytoreductive surgery. PET imaging is rarely utilized in the initial diagnostic phase because its effectiveness is restricted in identifying small-volume and diffuse miliary peritoneal diseases due to variations in lesion size and the background PET activity from the bowels/bladder. PET scans are usually reserved for cases with uncertain findings on CT/MR scans, especially those that might hinder primary surgery or in situations of recurrence [10].

However, the clinical manifestations, imaging results, and tumor marker results provide an insufficient basis for NACT, with pathological evidence also needed. Freedman *et al*. [11] performed a retrospective study of 149 patients with advanced EOC from 1994 to 2007. These authors found that diagnosis of EOC based on cytological and histological criteria gave better results than clinical factors alone (i.e., radiology, CA-125, clinical presentation). The diagnostic accuracy of pleural fluid cytology, histology, and clinical factors as confirmed by cytoreductive surgery was 98%, 92% and 87%, respectively. Onda *et al*. [12] reported on 56 patients with stage III/IV ovarian cancer diagnosed according to clinical manifestations, imaging findings, tumor markers, pleural and ascites cytology. These were confirmed to have ovarian cancer through diagnostic laparoscopy, with a diagnostic accuracy of 100% and a staging accuracy of 95%. In a retrospective study of 60 patients, 47 of whom received surgery, Schwartz *et al*. [13] assessed the value of ascites cytology for diagnosing AOC prior to NACT. The cytological results indicated ovarian cancer in 55 patients, absence of ovarian cancer in 4 cases, and indeterminate in one case. Among 43 patients with ascites cytology results indicative of ovarian cancer, 42 were confirmed by postoperative pathological examination, while one showed no pathological evidence of the disease. Of the three patients whose ascites cell examination results were not considered as ovarian cancer before treatment, two were confirmed as ovarian cancer by postoperative pathological examination, and one was confirmed as renal cancer. The patient with inadequate cytology for diagnosis also had an EOC detected at the time of diagnosis. Onda *et al*. [14] carried out a randomized controlled trial (RCT) that compared computed tomography staging with surgical-pathological the International Federation of Gynecology and Obstetrics (FIGO) staging for patients in the PCS arm. For surgical stage III disease involving extra-pelvic peritoneal disease and/or retroperitoneal lymph node metastasis, computed tomography staging achieved a positive predictive value and sensitivity of 99%. However, the positive predictive values were notably low ($<$20%) for the detection of small ($\leq$2 cm) extra-pelvic peritoneal disease in the omentum. Wang *et al*. [15] used *PAX8* and calretinin to stain 168 cytology specimens from patients who were susceptible to ovarian cancer (n = 96), patients with metastatic cancer (n = 22), and benign controls (n = 50). Of the 96 ascitic samples before NACT, 76 (79%) exhibited morphological characteristics consistent with ovarian primary cancers. These were all positive for *PAX8* and negative for calretinin. The remaining 20 cases (21%) could not be further classified, even though they tested positive for adenocarcinoma. Of the 22 cases of pelvic metastatic cancer, one *PAX8* positive and calretinin negative case was a renal cell carcinoma. The other 21 cases were *PAX8* negative and calretinin negative, and comprised 4 cases of breast metastasis and 17 cases of gastrointestinal tract metastasis. In the benign control group of 50 cases of pelvic washing, 5 *PAX8* positive and calretinin negative cases indicated endosalpingiosis (n = 4) and endometriosis (n = 1), while 25 *PAX8* negative and calretinin positive cases showed reactive mesothelial cells. The remaining 20 specimens were *PAX8* negative and calretinin negative, and typically contained inflammatory or blood cells without noticeable diagnostic epithelial features.

After diagnosis of ovarian cancer, the likelihood of complete cytoreductive surgery after NACT should also be predicted. Laparoscopy serves as a reliable method for evaluating the extent of disease and anticipating the feasibility of disease removal. ‘Fagotti score’ based on peritoneal carcinomatosis, omental cake, diaphragmatic involvement, bowel or gastric infiltration, mesenteric retraction and liver metastases, was introduced in 2006 to predict

the chances of optimal cytoreduction in AOC patients [16]. In the research, 64 patients underwent both laparoscopy and longitudinal laparotomy. Seven laparoscopic parameters were identified and linked to numerical variables based on the strength of their statistical associations. The presence of omental cake, peritoneal carcinosis, diaphragmatic carcinosis, mesenteric retraction, bowel and/or stomach infiltration, and liver metastases met the fundamental inclusion criteria and were attributed a definitive predictive index value of 2. In the final model, a predictive index score of $\geq$8 accurately pinpointed patients undergoing suboptimal surgery, demonstrating a specificity of 100%. The positive predictive value (PPV) was 100%, while the negative predictive value (NPV) stood at 70%. After the introduction of upper abdominal surgery, the overall accuracy of 'Fagotti score' was confirmed [17].

'Fagotti score' assists doctors in accurately assessing the extent of ovarian cancer lesions before surgery, identifying patients suitable for complete cytoreduction after NACT. This helps doctors devise treatment plans, increasing the chances of successful surgery and improving patient survival outcomes.

In conclusion, CT exhibits limitations in diagnosing ovarian cancer, whereas MRI and DWI-MRI demonstrate higher accuracy. Pleural/ascites aspiration cytology is a reliable method for the accurate diagnosis of ovarian cancer prior to NACT. Preoperative computed tomography staging can substitute for surgical-pathological diagnosis of patients with stage III ovarian cancer receiving NACT, but has insufficient reliability for diagnosis of stage IIIB disease. *PAX8* detects all Müllerian-derived benign or malignant epithelia. In cases where *PAX8* is incorporated with calretinin, it becomes an effective indicator for diagnosing ovarian cancer. After diagnosis of ovarian cancer, 'Fagotti score' can help identify patients suitable for complete cytoreductive surgery after NACT.

4. Treatment with NACT

The commonly used chemotherapy regimen for advanced EOC is paclitaxel combined with carboplatin or cisplatin. Both these chemotherapy regimens have comparable efficacy for the treatment of EOC [18]. Early incorporation of bevacizumab has been approved for carefully chosen, high-risk patients who need NACT for initially unresectable ovarian cancer. Garcia *et al*. [19] performed a phase II trial of 68 patients who were randomly assigned to chemotherapy alone (n = 33), or with bevacizumab (n = 35). The addition of 3 to 4 cycles of bevacizumab to NACT before surgery for irremovable disease did not improve the rate of complete macroscopic response or surgical outcome. However, it did enhance surgical operability and reduce the occurrence of grade 3 or more adverse events. Hence, the addition of bevacizumab to a preoperative regimen in patients considered not initially resectable appears to be safe.

Following the standard platinum-based first-line chemotherapy, maintenance therapies involving poly (ADP-ribose) polymerase inhibitors and antiangiogenic agents have proven effective for patients with AOC [20]. Olaparib or niraparib maintenance therapy seems to be the better option for patients with *BRCA1/2* mutations. Niraparib monotherapy and olaparib combined with bevacizumab have shown considerable advantages in progression-free survival (PFS) in homologous recombination deficiency (HRD)-positive patients. *SOLO-1* conducted by Moore *et al*. [21] aimed to evaluate the effectiveness and safety of olaparib maintenance therapy (300 mg, twice daily) in patients with advanced FIGO stage III or IV high-grade serous or endometrioid ovarian cancer. These patients had a mutation in either *BRCA1*, *BRCA2*, or both and had achieved a complete or partial clinical response following platinum-based chemotherapy. The participants possessed either germline or somatic *BRCA1/2* mutations, significantly benefited from olaparib maintenance therapy. PRIMA (a study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy [September 2019]) conducted by González-Martín *et al*. [22] was a double-blind, placebo-controlled phase III trial, investigating the safety and efficacy of niraparib therapy in patients with advanced FIGO stage IIIB–IIIC, stage IV, high-grade serous, or endometrioid ovarian, primary peritoneal, or fallopian tube cancer who were at a higher risk of recurrence, irrespective of *tBRCAm* status, after responding to initial platinum-based chemotherapy. The study revealed a substantial enhancement in PFS with niraparib, both in the HRD-positive subgroup (21.9 *vs.* 10.4 months) and the overall population (13.8 *vs.* 8.2 months) when compared to the placebo. Niraparib monotherapy demonstrated enhanced PFS in HRD-negative patients, indicating it could serve as a substitute for bevacizumab in HRD-negative patients. Ray-Coquard *et al*. [23] conducted *PAOLA-1* which was a randomized, double-blind study exploring the combination of olaparib (300 mg, twice daily) and bevacizumab as maintenance therapy after initial treatment in patients newly diagnosed with advanced FIGO stage III, high-grade serous, or endometrioid ovarian, primary peritoneal, or fallopian tube cancer. This treatment approach was applied regardless of the patients' *BRCA* status, as long as they achieved either complete response or partial response following standard first-line platinum–taxane-based chemotherapy and bevacizumab. The study demonstrated significant progress in PFS, particularly in patients with *BRCA* mutations (37.2 *vs.* 21.7 months) and those showing positive HRD status, including *tBRCA* mutations (37.2 *vs.* 17.7 months). An RCT conducted by Harter *et al.* [24] found that introducing maintenance olaparib alongside bevacizumab resulted in significantly improved PFS for patients with newly diagnosed AOC, especially in the subgroup with

positive-HRD. González-Martín *et al.* [25] conducted a phase 3, double-blind, placebo-controlled study. Patients with newly diagnosed AOC who had achieved complete or partial response to first-line, platinum-based chemotherapy were randomly assigned to receive either niraparib or a placebo once daily (2:1 ratio). Over a follow-up period of 3.5 years, niraparib showed significant and clinically relevant improvement in PFS for patients who were at high risk of progression, regardless of their HRD status.

There is an ongoing debate concerning the ideal number of cycles. Retrospective studies have indicated that patients subjected to prolonged NACT cycles experience poorer results [26,27]. Lim *et al.* [28] conducted a study involving 30 patients with stage III/IV ovarian cancer. Their findings revealed that administering >3 cycles of NACT did not increase the patients' response to chemotherapy, but increased toxic side effects. If too many cycles of NACT are administered prior to surgery, there is concern about the potential development of post-surgical chemoresistance. A meta-analysis found a correlation between adverse overall survival (OS) and the number of NACT cycles administered [29]. Loizzi *et al.* [30] retrospectively studied 30 patients with NACT from 1994 to 2003. These authors reported there was no statistically significant difference in outcome between patients who received $\leq$3 courses of NACT compared to those who received >3 courses. However, findings from other studies suggest that six or more cycles of NACT later allowed more extensive complete resections by ICS. Kumari *et al.* [31] compared 3 and 6 cycles of NACT for achieving optimal cytoreduction in patients with advanced stage IIIc/IV EOC, fallopian tube cancer, and primary peritoneal cancer. Administering 6 cycles of NACT before surgery was found to increase 10-fold the likelihood of achieving optimal cytoreduction compared to the administration of 3 cycles. This difference was statistically significant. Another study conducted by Kondo *et al.* [32] found that at least 6 cycles of NACT combined with ICS reduced the likelihood of multi-organ resection and increased the frequency of complete resection or optimal outcomes (<1 cm) after ICS. Therefore, the optimal number of cycles for NACT is likely to be 3 or 4.

5. When to Perform ICS and What is the Target?

Few RCTs focused on NACT have carefully examined the time to surgery (TTS), with many studies not even stipulating a suggested time interval. It is generally agreed that ICS should be performed once clinical recovery from neutropenia has occurred. However, a variety of non-clinical factors can delay ICS in real-world situations [33]. Prior studies have published contradictory results on whether this delay adversely impacts survival in ovarian cancer. Lee *et al.* [34] figured out that minimizing the time interval was found to potentially improve patient outcomes. Chen *et al.* [35] confirmed no correlation between the NACT to surgery interval and OS, while noting an adverse impact on PFS when the TTS exceeded 4 weeks. Liu *et al.* [33] reported that postponement of ICS following the completion of NACT negatively affected OS without influencing PFS. These results suggest that minimizing ICS delays could potentially improve outcomes for ovarian cancer patients treated with NACT. Conversely, Liu *et al.* [36] found that the timing of ICS was not significantly associated with prognosis.

The definition of optimal cytoreduction given by the Gynecologic Oncology Group is residual disease with a maximal residual tumor diameter of 1 cm [37]. However, NACT may increase the possibility of chemoresistance in ovarian cancer cells [3], and the number of chemotherapy courses after NACT is less than that after primary surgery. Therefore, the criteria for satisfactory tumor reduction in ICS should be more stringent than that for PCS. The size of postoperative residual tumor is known to significantly affect the prognosis of AOC patients. A meta-analysis showed that for each 10% increase in maximal cytoreduction, there was a corresponding 5.5% increase in median survival, thus affirming the positive outcomes associated with maximal cytoreduction [29]. Multiple studies have consistently shown that the most favorable results are obtained when cytoreduction leads to no visible residual disease [38–41]. Therefore, in order to improve prognosis, the standard for satisfactory tumor reduction during ICS should be no visible residual disease.

6. Challenges with ICS

The challenges for ICS in treating advanced EOC involve several complex considerations and technical aspects. These are described below in detail.

6.1 Extent of Residual Disease

As discussed previously, to improve prognosis the standard for satisfactory tumor reduction during ICS should be no visible residual disease. This often requires meticulous surgical skills, including advanced laparoscopic or open surgical techniques.

6.2 Tissue Fibrosis

NACT can lead to tumor fibrosis [42], making it more difficult to distinguish between healthy and cancerous tissue during surgery. Doctors must carefully navigate these fibrotic areas in order to avoid causing injury or leaving behind residual disease.

6.3 Adhesions

NACT may result in the formation of adhesions, which can pose challenges in terms of access to the abdominal cavity and visualization during surgery. Surgeons must be adequately prepared to manage these adhesions and to skillfully dissect tissue layers, thereby ensuring a safe and effective operation.

6.4 Multivisceral Surgery

Patients may require extensive multivisceral surgery. This involves the removal of tumor masses that have invaded nearby organs. Performing these procedures safely and effectively requires a high level of surgical expertise.

6.5 Minimally Invasive Surgery

Minimally invasive techniques, such as laparoscopy, are increasingly used in post-NACT surgery to reduce surgical trauma and enhance recovery. However, these procedures can be technically demanding and require specialized equipment and training.

6.6 Risk of Complications

Post-NACT surgeries are associated with a higher risk of complications due to factors such as tissue fragility, fibrosis, and adhesions. Surgeons must be prepared to manage potential complications during and after surgery, including bleeding, infection, and bowel injuries.

Overall, ICS is a highly specialized field in gynecologic oncology that requires a combination of surgical skill, experience, and multidisciplinary collaboration to optimize patient outcomes, while also managing the unique challenges associated with ICS.

7. Evaluation of the Pathomorphological Response to NACT

Discernible microscopic changes such as tumor necrosis, fibrosis, infiltration of macrophages, and tumor-induced inflammation have been reported as a result of tumor response to NACT [42]. These alterations are valuable for determining prognosis and for guiding future treatment decisions.

Böhm *et al*. [43] proposed a three-tier chemotherapy response score (CRS) system to evaluate patients treated with NACT followed by ICS. This system is based on the assessment of adnexal and omental sections.

CRS 1 indicates an absence of, or minimal tumor response, with few or insignificant regression-associated fibroinflammatory alterations limited to a few small areas of primarily viable tumor. In addition, there are cases where it is difficult to distinguish between regression and tumor-associated desmoplasia, or infiltration with inflammatory cells.

CRS 2 represents a substantial tumor response in easily recognizable viable tumor tissue; widespread or scattered regression-related fibroinflammatory changes accompanied by viable tumor in layers, streaks, or nodules; and extensive regression-related fibroinflammatory changes with easily distinguishable multifocal residual tumor.

CRS 3 signifies a complete or near complete response, with the absence of any residual tumor; minimal irregularly scattered tumor foci, appearing as individual cells, cell groups, or nodules with a maximum size of up to 2 mm; primarily regression-associated fibroinflammatory changes; and an almost complete absence of residual tumor without any significant inflammatory response.

The above CRS system demonstrated strong reproducibility (kappa, 0.75), and reliably predicted PFS after accounting for age, stage, and cytoreductive status. CRS 3 also predicts the responsiveness to initial platinum therapy. The International Collaboration on Cancer Reporting, and the College of American Pathologists guidelines include CRS for the histologic reporting of ovarian cancer [44]. Furthermore, this system has undergone successful validation in multiple studies [45–48].

The incorporation of pathologic response as a prospective surrogate endpoint for drug development may be immensely beneficial. In this regard, the integration of a straightforward, cost-effective, and reproducible scoring system into routine histological reports could provide valuable prognostic insights and potentially advance the personalization of treatments.

8. Changes in the Tumor Microenvironment during NACT

Tumor-infiltrating lymphocytes (TILs) have been implicated in the control of tumor growth [49] and have been consistently associated with better survival in EOC [50]. The emergence of therapeutic strategies that aim to mobilize tumor-reactive TILs is therefore very appealing. Evaluation of changes in the immune infiltrate during NACT may provide novel insights for the application of immunotherapy as a maintenance strategy after primary treatment.

Cao *et al*. [51] used multiplex immunofluorescence to investigate the tumor immune environment (TIME) of treatment-naive EOC tumors. These authors correlated the TIME status pre- and post-platinum-based NACT with treatment effectiveness and prognosis in 33 patients with advanced EOC. The density of immune cells within tissue specimens was found to increase significantly after NACT, including CD8+ T cells, CD20+ B cells, CD56 NK (natural killer) cells, PD-1+ cells, and PD-L1+CD68+ macrophages. CA-125 response and CRS were used to evaluate the response to NACT. Compared to non-responders, tumors from responders showed increased infiltration with CD20+ cells, a higher classically activated macrophages/alternatively activated macrophages (M1/M2) ratio, and less infiltration with CD56 bright cells. No correlation was observed between the pre-NACT TIME and response to NACT. The density of CD8+ cells before NACT was positively correlated with better PFS and OS. Post-NACT levels of infiltration with CD20+ and CD163+ macrophages (M2) were associated with longer and shorter PFS, respectively. Higher CD4+ T cell density was associated with better PFS and OS. Multivariate analysis showed that a higher density of pre-NACT CD8+ cells was independently associated with longer OS.

Leary *et al*. [52] investigated the effect of NACT on immune subpopulations, with a particular focus on the equilibrium between immune-reactive and immune-tolerant subgroups. Immunohistochemistry was performed on tissue microarrays of 145 pre-NACT and 139 post-NACT EOC samples. These were analyzed for the presence of CD3+, CD8+, FOXP3+ (forkhead/winged helix transcriptional factor P3), CD68+, and CD163+ cells, and the CD4+ cell count was deduced. NACT caused a marked increase in stromal CD3+ and CD8+ infiltration, as well as intra-epithelial CD8+ and CD68+ infiltration both in unmatched samples and within paired samples for stromal CD3+ and CD8+. The expression levels of CD3+, CD8+, CD4+, CD68+ and CD163+, either during diagnosis or after NACT, did not correlate with outcome. Using the median value as a threshold, high post-NACT ratios of stromal CD8+/FOXP3+ and of stromal CD3+/FOXP3+ were linked to prolonged PFS. This correlation suggests the shift towards a more favorable balance between effector and regulatory TILs was associated with improved survival. Similarly, a high CD68+/CD163+ ratio post-NACT contributed to improved PFS.

The results from these studies could potentially identify novel predictive markers for treatment efficacy and survival. Furthermore, they could reveal novel pathways, mechanisms, and biomolecules in advanced EOC that could be targeted simultaneously in novel treatment combinations to improve disease control.

9. Platinum Resistance of NACT

Although chemotherapy is effective at targeting and killing cancer cells, some cells may develop drug resistance over time, lead to the survival and proliferation of chemo-resistant clones within the tumor, thereby resulting in a more aggressive form of cancer and worse prognosis.

Shen *et al*. [53] employed single-cell RNA sequencing to analyze pre-NACT multi-site tumor tissue samples and post-NACT multi-site tumor tissue samples from a single case of advanced, high-grade serous fallopian tube carcinoma. Distinct characteristics were identified among the tumor, immune, and stromal cell types between the pre-NACT and post-NACT tumors. Notably, the malignant epithelial cells exhibited a higher level of intratumor heterogeneity in response to NACT. The primary resistant clone, designated as clone 63, had an epithelial genotype. It was pre-existing in the pre-NACT tumor samples and was subsequently enriched following NACT. Furthermore, clone 63 exhibited a strong association with unfavorable clinical prognosis.

Li *et al*. [54] identified the top genes related to platinum-resistance based on text mining (*TP53, ABCB1, AKT1, ERCC1, BCL2, EGFR, BRCA1, PIK3CA, MAPK1, ABCC1, IL6, NFKB1, STAT3, MTOR, PARP1, TNFSF10, BRCA2, HDAC1, TNF*). They also conducted gene ontology analysis to investigate the potential roles of these genes. Apoptosis emerged as the most prominent process, with signal transduction, cell communication, cell cycle, anti-apoptosis, and nucleobase and nucleic acid metabolism also being notable. These authors also created a protein-protein interaction network in order to identify significant molecules in the mechanism of platinum resistance. *TP53* exhibited the highest degree of interaction amongst the proteins, highlighting its crucial role in regulating platinum resistance. In addition, HSP90AA1, ESR1, AKT1, BRCA1 and several other proteins were identified as significant hubs within the signaling network. Cluster analysis highlighted specific genes within each subtype of ovarian cancer, suggesting that different subtypes may harbor unique mechanisms of resistance.

Platinum resistance poses a significant challenge in the treatment of EOC. Exploring the molecular mechanisms responsible for platinum resistance in EOC and identifying the regulatory genes and pathways involved may provide valuable insights and serve as a foundation for future drug research and development efforts.

10. Conclusions

NACT is a crucial strategy in the treatment of AOC. Although the debate concerning the effect of NACT on the prognosis of AOC still needs to be resolved, the likelihood of achieving satisfactory tumor reduction is increased with NACT, thus improving the patients' survival outcome. With ongoing research and especially more multicenter prospective RCTs, additional evidence should be forthcoming to establish the utility of NACT in the treatment of AOC.

Abbreviations

EOC, epithelial ovarian cancer; AOC, advanced ovarian cancer; NACT, neoadjuvant chemotherapy; ICS, interval cytoreductive surgery; PCS, primary cytoreductive surgery; PFS, progression-free survival; OS, overall survival; CA-125, cancer antigen 125; HE4, human epididymis protein 4; ROMA, risk of ovarian malignancy algorithm; CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; PET-CT, positron emission tomography–computed tomography; DWI, diffusion-weighted imaging; FIGO, the International Federation of Gynecology and Obstetrics; TILs, tumor-infiltrating lymphocytes; HRD, homologous recombination deficiency; TTS, time to surgery; CRS, chemotherapy response score; TIME, tumor immune environment; RCT, randomized controlled trial.

Author Contributions

JL: Contributions to the conception and design of the work, retrieval, review, and analysis of literature, specifically writing the initial draft. JZ and SL: Contributions to the conception and design of the work, specifically critical

review, commentary or revision – including pre- or post-publication stages. CB: Contributions to the conception and design of the work, responsible for protocol development, manuscript editing, and given final approval of the version to be published. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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