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Management of Advanced Ovarian Cancer: A Brief Insight into the Role of Neoadjuvant Chemotherapy Followed By Interval Debulking Surgery

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Abstract

Ovarian cancer is a fatal gynecologic cancer and ranks as the seventh most common cancer in women worldwide. It can affect women of all ages but is typically seen in between 55-64 years. With no specific early signs and symptoms, most patients are diagnosed at a late stage and thus, associated with high mortality. The diagnosis is only confirmed pathologically following surgery or by cytological evaluation. Surgery accompanied by adjuvant chemotherapy has been the standard approach for managing ovarian cancer. However, the majority of the patients cannot undergo primary debulking due to old age, poor quality of life, huge tumor burden and ascites. Thus, over the recent years, neoadjuvant chemotherapy (NACT) accompanied by interval debulking surgery (IDS) has shown incredible results in the management of advanced ovarian cancer, especially in patients unfit for undergoing primary debulking. The progression-free survival between primary debulking surgery and NACT accompanied by IDS were reported almost similar with a lesser rate of perioperative morbidity and mortality reported in patients under NACT treatment regimen. Residual disease is a significant factor determining the patient's prognosis in ovarian cancer and various studies have reported that NACT treatment regimen helps to achieve a better rate of optimal cytoreduction and hence improves the quality of life. Proper selection of patients would be advantageous in individualizing the treatment regimen, which would help in improving patient's prognosis. Although there are strong evidences advocating for NACT treatment regimen, still some doubts exist and further research is still warranted.

Introduction

Ovarian cancer, the principal cause of cancer-related death in women with gynecological malignancy, has estimated incidences of 238700 cases worldwide with estimated deaths of 151900 annually [1, 2]. In China, the estimated annual incidence was 52100 with estimated deaths of 22500 in 2015 [3]. It is normally seen in ages between 55-64 years. Epithelial ovarian cancer (EOC), the most common type of ovarian cancer, accounts for 90% of the patients followed by the germ cell tumor (5%) and the sex cord-stromal tumor (rare) [4]. There are no early reliable methods for detecting patients with ovarian cancer and thus, patients often present at a late and advanced stage, thus, is associated with high mortality [4, 5]. Diagnosis is confirmed only after surgery (open or laparoscopic procedure) or by sampling of the tissue or ascetic fluid [4, 5]. Recent guidelines for evaluating ovarian cancer provided by the American Society of Clinical Oncology (ASCO) and the Society of Gynecology Oncology (SGC) recommend "performing a Computed Tomography (CT) scan of abdomen and pelvis with oral and intravenous contrast and chest imaging (most preferably CT scan of chest) to evaluate the degree of disease spread for staging and for individualizing the treatment regimen [6]." Staging is done following surgery as per the International Federation of Gynecology and Obstetrics (FIGO) staging system [6].

Primary debulking surgery (PDS) in conjunction with adjuvant chemotherapy has been the standard approach for managing ovarian cancer for decades and surgery normally involves removal of the uterus, cervix, ovaries, fallopian tubes and omentum with lymph node resection (pelvic and para-aortic lymph nodes), and other procedures, such as appendectomy, when indicated [7,8]. However, there is a high occurrence of relapse within the first five years with no noteworthy progress in the five-year survival rate. Most ovarian cancer patients are elderly with comorbid conditions and a large tumor with huge ascites which makes them less suitable for undergoing primary debulking surgery [9, 10]. Recently, neoadjuvant chemotherapy (NACT) accompanied by interval debulking surgery (IDS), has shown incredible promise in managing patients unsuitable for primary debulking, thus, has been considered as a better substitute to primary debulking surgery. Several studies have shown the overall survival (OS) and progression-free survival (PFS) are almost comparable between NACT treatment strategy and primary debulking surgery accompanied by adjuvant chemotherapy treatment, thus, vouching for the NACT treatment plan as it has been gaining credibility in the treatment of advanced ovarian cancer [10-12]. In this article, we outlined the latest knowledge, benefits of NACT accompanied by interval debulking surgery in managing advanced ovarian cancer.

NACT strategy in ovarian cancer patients with advanced disease

Optimal surgical debulking is achievable in only 30-60% of ovarian cancer patients with advanced disease (stage IIIc/IV), thus the residual tumor following surgery is fundamental in patient's prognosis [13]. In 1975, Griffiths reported the patient's survival time was inversely associated with residual tumor (under 1.6 cm) in ovarian cancer patients, thus, emphasizing the importance of achieving optimal cytoreduction [14]. The description of the term "optimal cytoreduction" has changed since Griffith's report and the current consensus for optimal cytoreduction is "to achieve an utmost residual disease of less than 1 cm in diameter with the main aim of leaving no macroscopic disease." Thus, the main principle of surgery (either primary debulking or interval debulking following NACT) is to acquire optimal cytoreduction and to get rid of all visible tumors [15-17]. Ovarian cancer is exceptionally responsive to chemotherapy with a 70%-80% response rate [18]. Van der Burg et al. reported benefits of administering chemotherapy (cisplatin and cyclophosphamide, three cycles) prior to undergoing interval debulking surgery in 140 stages IIb-IV ovarian cancer patients who had suboptimal cytoreduction following primary debulking surgery by comparing it with 138 stages IIb-IV ovarian cancer patients who continued chemotherapy in 1995. They reported NACT treatment regimen improved overall survival (median survival: 26 months for NACT followed by interval debulking surgery and 20 months for patients who continued chemotherapy) and progression-free survival (18 months for NACT followed by interval debulking surgery and 13 months for patients who continued chemotherapy) [19]. This study highlighted the potential benefits of NACT accompanied by interval debulking surgery in advanced ovarian cancer patients as it could aid in reducing the burden of the disease by decreasing the size of the tumor and ascites, thus, making optimal cytoreduction achievable [20-21].

A retrospective study involving 285 advanced ovarian cancer patients conducted between 1980 to 1997 [first period 1980-1988: PDS, second period 1989-1997: PDS (57%), NACT/IDS (43%)], Vergote et al. compared the patients receiving NACT (three courses) accompanied by IDS with patients undergoing PDS and reported overall survival in NACT treatment strategy was better than PDS (first period 3 year survival 26% versus second period 3 year survival 42%). Thus, they summarized NACT treatment option was a good alternative in ovarian cancer patients with advanced disease (stage IV), metastasis, poor performance status etc. [22]. In another study, Kayikçioğlu et al. evaluated 203 stage III /IV epithelial ovarian cancer patients by comparing 158 patients undergoing PDS with 45 patients undergoing NACT treatment strategy. They noted the five-year survival and median survival were comparable in patients undergoing NACT treatment plan (5-year survival 30% with median survival 34.1 months) and the patient undergoing PDS (5-year survival 24% with median survival 37.9 months). The disease-free survival [PDS: 16.03 months, median 12 months; NACT + IDS: 13.9 months, median 13.9 months] and the overall survival [PDS: 27.6 months, median 25 months; NACT + IDS: 19.9months, median 18 months] were statistically comparable [23]. Numerous studies have come to a similar conclusion of overall survival and progression-free survival was almost statistically similar between NACT treatment strategy and PDS treatment strategy, further backing the NACT treatment strategy in managing advanced ovarian cancer [24-28].

Despite strong evidence advocating for the NACT treatment strategy, there are still doubts about it. Rose et al. evaluated the benefits of undergoing IDS following chemotherapy (three cycles) with chemotherapy alone in ovarian cancer patients with advanced disease who had a residual tumor (>1 cm in diameter) following primary debulking. They concluded no significant enhancement in the progression-free survival and overall survival following IDS (median duration of survival: 33.9 months NACT + IDS group versus 33.7 months chemotherapy-alone group) [29]. A meta-analysis was done by Bristow and Chi also concluded NACT treatment plan was linked to reduced overall survival than PDS [30]. Later, a randomized controlled trial (RCT) was conducted by Vergote et al. and compared 670 ovarian cancer patients with advanced disease (stage IIIC/IV) undergoing PDS (336 patients) and NACT accompanied by IDS (334 patients). The median overall survival (NACT + IDS: 30 months versus PDS: 29 months) and progression-free survival (NACT + IDS: 12 months versus PDS: 12 months) was almost comparable in both with the postoperative mortality higher in the PDS group. Thus, they concluded, "NACT treatment strategy was non-inferior to PDS in advanced ovarian cancer [31]." Another randomized controlled trial carried out by Kehloe et al. (CHORUS trial) also compared 550 eligible advanced ovarian cancer patients undergoing PDS (276 patients) and NACT treatment strategy (274 patients). The median overall survival [NACT + IDS: 25.8 months versus PDS: 23.7 months] and progression-free survival [NACT + IDS: 12 months versus PDS: 10.7 months]. Postoperative complications were more frequent in PDS group than NACT group (24.1% PDS versus 14.1% NACT + IDS).They also noted residual disease was crucial in patient prognosis for both PDS and NACT accompanied IDS and hence, concluded NACT treatment plan was comparable to PDS in terms of overall survival and should be contemplated in ovarian cancer patients with advanced disease with comorbid conditions (poor performance status) as it leads to improvement of quality of life with reduced morbidity and mortality [32].

A phase III noninferiority trial (JCOG0602) governed by Japan Clinical Oncology Group (JCOG) involving advanced ovarian cancer patients undergoing PDS and NACT treatment strategy has recently published their interim analysis results and concluded NACT accompanied by IDS being less invasive than PDS. The NACT group of patients required less surgeries [mean 0.82 (NACT + IDS) versus 1.32 (PDS)], lesser frequency of resection of abdominal organ (23.7% NACT versus 37.6% PDS) and less frequency of severe side effects (4.6% NACT versus 15% PDS) [33]. Another phase III randomized controlled trial (SCORPION trial NCT01461850) has also released their initial analysis results in relation to safety (perioperative morbidity and mortality) in epithelial ovarian cancer patients with high tumor burden undergoing either PDS or NACT treatment strategy. They have concluded NACT accompanied by IDS was related to statistically significant lower risk of severe perioperative morbidity than PDS (postoperative complication rates 52.6% PDS versus 6.0% NACT + IDS; postoperative mortality rate 3.6% PDS versus 0% NACT + IDS) [34]. However, the results of the overall survival of both trials are still awaited

and their results may further enhance the credibility of NACT and IDS treatment strategy in advanced ovarian cancer patients.

Benefits provided by NACT treatment strategy

The role of NACT accompanied by IDS has gained recognition in the management of ovarian cancer patients with advanced disease as it provided certain benefits favoring it over PDS. NACT followed by IDS has almost a similar overall survival and progression-free survival to PDS and some studies have even suggested that NACT followed by IDS may become the new standard approach for managing ovarian cancer with advanced disease [33-34].

Optimal cytoreduction

Proper selection of a patient for individualizing the mode of treatment strategy is important as it helps in achieving optimal cytoreduction, thus, improving the patient's prognosis. NACT accompanied by IDS treatment strategy may help to achieve the optimal cytoreduction better than PDS in elderly patients with poor performance status, a large tumor with massive ascites and therefore, resulting in improved overall survival [35]. Kang et al. reported the risk of suboptimal debulking was 0.5 (95% CI, 0.28-0.86) in the NACT treatment plan in comparison to the PDS group. Therefore, they concluded NACT accompanied by IDS was helpful in achieving an improved rate of optimal cytoreduction, especially in older age patients with comorbid conditions (poor performance status), huge tumor, and high risk of suboptimal debulking [36].

Improved perioperative morbidity and mortality

The NACT treatment plan has been considered less invasive than PDS [33-35]. In a study by Hegazy et al., total blood loss, duration of ICU and hospital stay was found to be notably lesser in the NACT group (mean blood loss 420 ml, mean ICU stay 1.7 days, mean hospital stay 10.5 days) than the PDS group (mean blood loss 735 ml, mean ICU stay 4.4 days, mean Hospital stay 15.9 days). There was an increased rate of optimal debulking in the NACT group than the PDS group (72.2% versus 62.4%) [37]. Similarly, Lee et al. also found the mean blood loss estimated was lower in the NACT group (620 ml) in comparison to the PDS group (1061 ml) with the mean postoperative stay 9.7 days for the NACT group and 10.4 days in the PDS group [38]. Giannopoulos et al. concluded the median intraoperative blood loss (500 ml NACT versus 1000 ml PDS), hospital stay (7 days NACT group, 8 days PDS group) and possible ICU stay (5.7 NACT/IDS versus 48.3 PDS) was considerably fewer in the NACT group than the PDS group [39]. A study by Zheng et al. also reported intraoperative blood loss (415 ml NACT versus 729.7 ml PDS) and blood transfusion (1.87 units NACT versus 2.97 unites PDS) was notably less in the NACT group compared to the PDS group [40]. Thus, NACT accompanied by IDS improves the perioperative mortality and morbidity and hence, resulting in early recovery and improving the overall quality of life.

Selection of patient for NACT/IDS

Although current evidence advocates for NACT treatment strategy, senior gynecologic oncologists (SGOs) still had their reservations. In a survey done by Dewdney et al. [41] and Hueslmann et al. [42], many senior gynecologic oncologists were still biased against NACT strategy in managing ovarian cancer with advanced disease and considered the evidence insufficient. Hacker et al. concluded PDS should remain the standard approach for managing ovarian cancer and patients with old age and comorbid conditions (poor performance status) would gain more from NACT treatment strategy [43]. However, the interim analysis results of the SCORPION trial [44] and JCOG0602 trial [45] suggest NACT accompanied by IDS being less invasive than PDS and hence, may become the new standard of care for the management of ovarian cancer patients with advanced disease. Thus, selecting patients benefiting from the NACT treatment strategy is important for better prognosis of the patient.

The capability to predict the residual disease following surgery or the likelihood of the achieving optimal cytoreduction in patients is the key in individualizing the mode of treatment, thus, preventing unnecessary exploratory laparotomy. Several studies have investigated the role of preoperative parameters preferably the radiological features to predict optimal cytoreduction; however, the results were varied [46-49]. Leuven criteria and the Essen criteria have been used by a gynecologic oncologist for the individualizing the treatment plan to achieve optimal cytoreduction [50]. Suidan et al. conducted a study involving 350 patients between 2001 and 2012 to assess computed tomography scan and CA-125's role in predicting residual disease. They identified 11 criteria (3 clinical and 8

Table 1 laparoscopic scoring system to predict optimal cytoreduction (Fagotti et al. 55-58).

Parameters	Score
Ovarian Masses (unilateral or bilateral)	0
Thickened greater omentum (Omental cake)	2
Peritoneal dissemination	2
Diaphragmatic dissemination	2
Mesenteric involvement	2
Infiltration of the bowel	2
Infiltration of the stomach	2
Metastasis to liver	2

Predictive Index Value (PIV) ≥8 distinguish patient likely to have suboptimal debulking.

radiological) which they considered being helpful in predicting residual disease and treatment plan. [51].

The role of laparoscopy has made headways in the field of medicine over the recent years and its role has been evaluated by several studies to predict optimal cytoreduction with many studies considering it a very reliable tool in ovarian cancer staging [52-54]. Fagotti et al. in a pilot study evaluated laparoscopy's role in predicting optimal debulking involving 95 ovarian cancer patients and concluded that it was accurate in predicting optimal cytoreduction (overall accuracy rate 90% with negative predictive value (NPV) of 73% on clinic-radiological evaluation versus 100% on laparoscopic evaluation) [55]. Later, Fagotti et al. evaluated the ability of the scoring system based upon the laparoscopy to predict optimal cytoreduction and to individualize treatment strategy in a study involving 64 advanced ovarian cancer patients. They identified eight laparoscopic parameters (Table 1) and concluded a predictive index value (PIV) of greater than or equal to 8 was able to distinguish patients likely to have suboptimal debulking with a positive predictive value (PPV) of 100% [56]. Again, Fagotti et al. used the laparoscopic scoring system they had proposed to predict optimal cytoreduction and planning of treatment in a prospective study involving 113 advanced ovarian cancer patients. A predictive index value of greater than or equals to 8 would distinguish patients probably to have suboptimal debulking. The overall accuracy of the procedure was 77.3%-100% and the rate of unnecessary exploratory laparotomy was 40.5%. Thus, they concluded the laparoscopic scoring system was reliable and accurate in predicting the optimal cytoreduction and individualizing the treatment plan [57]. Fagotti et al. also evaluated the laparoscopic staging scoring system for ovarian cancer patients with advanced disease and concluded that it was helpful in preventing unnecessary laparotomy, surgical complications and planning of treatment [58].

The American Society of Clinical Oncology (ASCO) and the Society of Gynecologic Oncology (SGO) presented a clinical guideline for individualizing the mode of treatment in patients with epithelial ovarian cancer with advanced disease (stage IIIC/IV) which has been widely accepted and very helpful in preventing unnecessary laparotomy and improving patient's prognosis. In the guidelines, they have recommended that primary evaluation of all patients with suspected advanced ovarian cancer should be done by a gynecologic oncologist and it should include a contrast-enhanced computed tomography scan of the abdomen and pelvis (oral and intravenous) along with chest imaging (if possible computed tomography of the chest). Further assessment [laparoscopic assessment or fluorodeoxyglucose positron emission tomography (FDG-PET)] may be added if required. All suspected patients should have histologically confirmed ovarian cancer either by core biopsy or cytological assessment combined with a cancer antigen 125 (CA-125) / carcinoembryonic antigen (CEA) ratio >25 to confirm the primary disease and rule out other non-gynecologic cancer before starting NACT regimen. If the tumor is potentially excisable in women fit for surgery, they should be given either the option of PDS or NACT with PDS being preferred over NACT if optimal debulking of less than 1 cm can be achieved with acceptable morbidity and NACT preferred over PDS in patients less likely of achieving optimal debulking of less than 1 cm. Hence, NACT should be considered in women with high risks (perioperative) or the low possibility of achieving debulking of less than 1 cm. [59].

Conclusions

Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) has gained incredible prominence in the treatment of advanced ovarian cancer over the recent years. Particularly, in elderly patients with poor performance status and massive ascites with huge tumor load, and has been considered non-inferior to primary debulking surgery with improvement in perioperative morbidity and mortality with an increased rate of optimal cytoreduction. With further research, it may eclipse standard conventional treatment of ovarian cancer and may become the new standard approach

in the management of ovarian cancer patients with advanced disease.

Conflict of Interest

All authors declare they have no conflict of interest

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