Do we have a new standard in suboptimal debulked disease?

M. A. Bookman* & Chair, Ovarian Committee, Gynecologic Oncology Group
University of Arizona Cancer Center, Tucson, USA

Treatment options for patients with high-risk advanced-stage ovarian cancer continue to evolve, including consideration of neoadjuvant chemotherapy (NACT), timing of cytoreductive surgery, utilization of intraperitoneal (IP) chemotherapy, adoption of dose-dense weekly paclitaxel (Taxol), addition of maintenance chemotherapy, and incorporation of bevacizumab. Overall, the proportion of patients with suboptimal residual disease has declined, partly as a result of more aggressive primary surgery, and partly through selection of patients for delayed surgery following NACT. However, the risk of recurrence in this population remains high, and treatment decisions need to be individualized, with consideration of clinical goals, avoidance of treatment-related toxicity, control of disease-related symptoms, and minimization of any negative impact on the quality of life. Innovative trials are needed to evaluate early predictors of primary platinum resistance and facilitate the development of non-platinum alternative treatment regimens.

Key words: cytoreductive surgery, neoadjuvant chemotherapy, ovarian cancer

introduction

In the setting of ovarian cancer with high-risk advanced-stage disease, there are a number of treatment options, including neoadjuvant chemotherapy (NACT) with interval cytoreductive surgery (ICS), intraperitoneal (IP) chemotherapy, dose-dense weekly chemotherapy, maintenance chemotherapy, and incorporation of bevacizumab. While individualized decisions arise based on the interpretation of data from randomized, phase III trials, the results are often extrapolated to patient populations not included in the original trial design, based on the clinical judgment, experience, and patient preference. This overview offers a paradigm for initial management of patients with high-risk disease, based on the synthesis of available data and clinical practice.

Surgical stage remains the most important prognostic factor [1, 2], and over 80% of newly diagnosed patients will have International Federation of Gynecology and Obstetrics stage III-C or IV tumors. The second most important prognostic factor is the extent of residual disease after primary cytoreductive surgery (PCS), with the greatest difference in long-term outcomes observed between patients with optimal microscopic disease (no visible residual) compared with optimal macroscopic or suboptimal residual disease [3]. Among patients who undergo initial cytoreductive surgery, ~80% achieve optimal cytoreduction, including ~25% within the most favorable (microscopic) subgroup. This leaves ~20% of patients with suboptimal residual disease.

However, with more sophisticated cross-sectional imaging techniques, and the increased acceptance of NACT and ICS, the population of patients who undergo PCS has become more highly selected, favoring patients with younger age, limited disease, small-volume ascites, and absence of comorbidities. As a result, older-aged patients with more extensive disease, high-volume ascites, and medical comorbidities are more likely to receive NACT. In addition, there has been a trend at some centers for patients to undergo more aggressive primary surgery, with an emphasis on upper abdominal procedures, including resection of multiple hepatic, diaphragmatic, splenic, and gastrointestinal metastases.

Taken together, these evolving clinical practices will tend to increase the rate of optimal cytoreduction achieved among those patients selected for primary surgery, leaving fewer patients with surgically documented suboptimal disease. These surgical decisions are largely based on the clinical judgment, as we do not have widely accepted criteria, based on the preoperative imaging or other factors, to define resectability, particularly with the adoption of more aggressive primary surgical techniques. Therefore, the present discussion of treatment options will focus on patients with extensive disease managed with NACT +/- ICS, as well as those with suboptimal residual disease following PCS.

optimal individualized therapy

Standards evolve as data from ongoing trials mature. The following considerations will be discussed from the perspective of existing data, clinical consensus, and practical experience.

goals of treatment

Patients who undergo NACT, and those with suboptimal residual disease following PCS, represent a population with extremely high-risk for recurrence, regardless of the outcomes.
of primary chemotherapy. As such, the goals of treatment are largely palliative, to improve disease-associated symptoms, delay recurrence, and maximize quality of life. From that perspective, it is important to minimize the risks associated with primary therapy, as there is no realistic chance of cure with currently available treatment options.

**selection of patients for NACT**

Two large, randomized trials have compared NACT-ICS with PCS in patients with advanced stage III and IV disease, achieving similar outcomes [4, 5]. Due to advanced disease status among enrolled patients, the median progression-free survival (PFS) and overall survival (OS) were poor, but with similar long-term outcomes on both treatment arms. Advantages associated with NACT include a reduction in perioperative morbidity related to venous thromboembolism, infection, transfusions, and wound healing, which are appealing in this population. Therefore, it is important to consider NACT for patients with advanced-stage disease, including bulky tumor deposits, large-volume ascites, advanced physiologic age, and other comorbidities.

**utilization of intravenous (IV) or IP chemotherapy**

Prior randomized studies have reported improved outcomes with IP chemotherapy in patients with optimal residual disease [6]. While IP therapy is feasible in patients with suboptimal residual disease [7], data are awaited from ongoing randomized trials (GOG0252 and JGOG) to determine whether IP therapy has any advantage in this setting, as well the potential substitution of IP carboplatin for IP cisplatin. At this point, IV chemotherapy is more commonly used in patients with suboptimal disease, but patients might also be considered for IP therapy after completion of NACT-ICS with small-volume residual disease, which is similar to the approach currently utilized in the ongoing NCIC-CTG OV21 trial.

**incorporation of bevacizumab**

Results from ICON7 and GOG0218 suggest that incorporation of bevacizumab will improve PFS, particularly in patients with bulky high-risk disease [8, 9]. A subpopulation analysis of ICON7 also suggested an improvement in median survival within a pre-defined high-risk population [10]. However, an advantage in OS was not initially observed in GOG0218, even though the majority of patients were enrolled with high-risk disease. The most likely explanation for this apparent discordance between the two trials is crossover to commercial bevacizumab post-progression, which was estimated at 30% in GOG0218, compared with essentially no crossover in ICON7. The optimal timing of bevacizumab administration is unknown, including concurrent treatment with primary chemotherapy, extended monotherapy (maintenance), or concurrent treatment in the setting of recurrent disease, and arguments can be made to support each of these options. However, while bevacizumab was generally well tolerated, all agents contribute to toxicity in this high-risk population, and there was clearly increased toxicity associated with concurrent chemotherapy and bevacizumab, compared with extended monotherapy. Randomized, phase III trials in the setting of platinum-sensitive [11] and platinum-resistant [12] recurrent disease have documented improved PFS with the incorporation of concurrent and maintenance bevacizumab. Taken together, in a patient population with suboptimal residual disease, it would be reasonable to plan primary therapy without bevacizumab, reserving bevacizumab for the setting of recurrent disease, when the benefit–risk ratio is maximized.

**choice of chemotherapy regimen**

All patients should begin with a combination of carboplatin and paclitaxel (Taxol), as there is no regimen with demonstrated superior performance [13, 14]. Within commonly established dose ranges, the absolute dose level is not critical, and it can be individualized depending on the vital organ function and tolerance. While it might be argued that single-agent carboplatin is safer and better-tolerated, that is an oversimplification, as the platelet-sparing effect of paclitaxel can facilitate cumulative dosing with carboplatin. Dose-dense weekly paclitaxel has emerged as a strong consideration, based on the JGOG3016 trial [15], and studies in recurrent breast and ovarian cancers also favor a weekly schedule of drug administration, on the basis of toxicity and efficacy. However, the use of 80 mg/m²/week (as in JGOG3016) is associated with frequent dose reductions and delays, due to hematologic toxicity, and there is also a risk of cumulative neurotoxicity, with ~40% of patients receiving less than six cycles of chemotherapy. Existing data do not support a dose–response relationship with either platinum agents or taxanes, within clinically relevant dose ranges, and the scheduling of paclitaxel appears to have a greater impact than the dose. Therefore, a dose of 60 mg/m²/week might be preferred in this high-risk population, but this has not been validated in a phase III trial. Of interest, the MITO7 trial used fractionated (weekly) carboplatin dosing, at targeted area under the curve (AUC) for concentration and time of 2 mg/ml/ min per week [16]. Initial analysis of PFS showed no statistically significant difference between weekly and three-weekly treatment, but favored weekly treatment based on the tolerability and reduced toxicity. Additional data are awaited from GOG0262, which utilized dose-dense paclitaxel together with conventional three-weekly carboplatin, similar to the JGOG3016 study. At the present time, it is reasonable to use weekly paclitaxel (60–80 mg/m²/week) with standard three-weekly carboplatin, to maximize efficacy and minimize toxicity.

**maintenance chemotherapy**

Following completion of primary chemotherapy, maintenance has been considered as a non-curative strategy to extend the duration of remission in a chemo-responsive population, although there is clearly an increased risk of cumulative toxicity. In the setting of advanced-stage ovarian cancer, all studies using chemotherapy have been negative [17, 18], with the exception of one study evaluating extended paclitaxel administered on a 3-week schedule [19]. After an early improvement in PFS, evident during a scheduled interim analysis, the study was closed to further accrual by recommendation of the data monitoring committee, compromising long-term clinical outcomes. The Gynecologic Oncology Group (GOG) is
currently completing a phase III maintenance trial (GOG0212) comparing observation with paclitaxel. Pending the results of that study, there is not currently any established role for maintenance chemotherapy in women with advanced-stage ovarian cancer.

**adjustment for physiologic age and comorbidities**

Most clinical trials of primary therapy have not enrolled a high proportion of older patients (above age 75), or patients with poor performance status and comorbidities. However, the GOG and other groups have been exploring feasibility and optimized dosing for older patients with and without comorbidities. Until guidelines from ongoing trials are available, it is reasonable to use conservative dosing, such as carboplatin with an AUC 5 mg/ml/min (as adjusted for renal function) and paclitaxel 135 mg/m² every 3 weeks, or paclitaxel 60 mg/m²/week.

**alternatives to standard platinum-based chemotherapy**

This is an important consideration for patients with high-risk disease, as ~20% will demonstrate disease progression during primary chemotherapy. There are alternative regimens that have similar front-line efficacy, such as carboplatin in combination with either docetaxel (Taxotere) or pegylated liposomal doxorubicin (PLD), but these would not be appropriate in the setting of primary platinum resistance. Depending on prior therapy, vital organ function, and performance status, individual patients could be managed with single agents, such as PLD, gemcitabine, weekly paclitaxel, or bevacizumab.

Development of new regimens remains a high priority for clinical trials, and this would be facilitated by collection of serial tumor specimens to define molecular patterns of treatment resistance, and utilization of functional imaging (CT, MRI, or PET) to provide an early biomarker of tumor progression, to permit rapid transition to alternative chemotherapy regimens.

**conclusion**

With advances in the selection of patients for cytoreductive surgery, together with more aggressive surgical effort, the proportion of patients with suboptimal residual disease will decline. In addition, more patients with high-risk disease are being considered for NACT, reducing the number of patients referred for PCS. Standard therapy for this population with advanced disease is largely based on the clinical judgment, extrapolated from existing phase III data. At present, the best option appears to be NACT with or without ICS, utilizing weekly paclitaxel and three-weekly carboplatin, with individualized doses based on the age, performance status, and comorbidities, without maintenance chemotherapy, and reserving bevacizumab for management of recurrent disease (Figure 1). Priorities for future studies include the development of alternative treatment regimens and functional biomarkers that predict for resistance to platinum-based chemotherapy.

**disclosure**

The author has declared no conflicts of interest.

![Figure 1](image.png)

**Figure 1.** Management of suspected high-risk advanced-stage disease. Includes suboptimal residual disease after primary cytoreductive surgery (PCS), or election of neoadjuvant chemotherapy with interval cytoreductive surgery. EOC, epithelial ovarian cancer; AUC, area under the concentration and time curve; PFI, platinum-free interval.


