What Is the Role of Neoadjuvant Chemotherapy in the Management of Ovarian Cancer?

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By Peter E. Schwartz, MD [1]

Conventional therapy for advanced-stage ovarian cancer—ie, aggressive cytoreductive surgery followed by aggressive chemotherapy—was established more than 3 decades ago [Editor’s note: See Dr. Schwartz’s article, “Cytoreductive Surgery in the Management of Ovarian Cancer,” in last month’s issue of ONCOLOGY]. Since that time, no prospective randomized trials have been reported to confirm the efficacy of this treatment strategy. Recent large retrospective studies have demonstrated that the greatest survival benefit is accrued to those who have no gross disease left after the initial surgical cytoreduction. This represents only 23% of stage III patients and 8% of stage IV patients.[1,2] Alternative strategies for patients who do not appear to be surgically cytoreducible to no macroscopic residual disease need to be identified.

One such strategy—chemotherapy administered prior to aggressive surgical cytoreduction, ie, neoadjuvant chemotherapy—is now being evaluated in three prospective randomized trials. Retrospective reports utilizing neoadjuvant chemotherapy suggest that a major benefit to this approach is a significantly higher rate of surgical cytoreduction to no visible disease. Additional benefits include a patient in a better nutritional state preoperatively than with conventional treatment. Surgery performed following neoadjuvant chemotherapy is routinely shorter in time, associated with less blood loss, shorter intensive care unit stays and shorter hospitalizations. Survival data suggest no difference in the progression-free or overall survival for stage III disease patients treated with neoadjuvant chemotherapy or conventional therapy. Some reports suggest improved survival with stage IV patients treated with neoadjuvant chemotherapy compared with conventional therapy.

This article will review the current status of neoadjuvant chemotherapy for the management of women with advanced-stage ovarian cancer.

History of Neoadjuvant Chemotherapy for Ovarian Cancer

Neoadjuvant chemotherapy as used in this article refers to the administration of chemotherapy for advanced-stage ovarian cancer prior to attempted surgical cytoreduction. This approach was first used at Yale University in 1979.[3] The diagnosis of ovarian cancer was based on a computed tomography (CT) scan consistent with advanced-stage ovarian cancer and cytology consistent with a nonmucinous epithelial ovarian cancer.[4]
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The initial approach used at Yale University was to reserve neoadjuvant chemotherapy for women who were medically impaired such that their performance status would not allow them to undergo aggressive cytoreductive surgery. A decade after its use in that regard, it was recognized that there were ovarian cancer patients who, by CT criteria, were unlikely to be optimally surgically cytoreduced.[5] Those patients were then offered neoadjuvant chemotherapy as the initial step in the management of their disease.

Neoadjuvant chemotherapy alone is insufficient for the initial treatment of advanced-stage ovarian cancer[5]—it is only one event in the treatment course. Aggressive cytoreductive surgery is the necessary next step. Surgeons who are unprepared for aggressive cytoreductive surgery should not be performing the surgery following neoadjuvant chemotherapy. Such surgery should be done by a gynecologic oncologist prepared to do radical surgery necessary to remove all gross disease present following neoadjuvant chemotherapy. Today, it is believed that the major value of neoadjuvant chemotherapy is in preparing patients for aggressive cytoreductive surgery so that those patients can be optimally cytoreduced.[6]

Patient Selection for Cytoreductive Surgery

Many attempts have been made to identify the patients unlikely to be optimally surgically cytoreduced. Diagnostic imaging has been employed. In 1993, Nelson et al published the Yale criteria for when patients are unlikely to be optimally cytoreduced.[7] These criteria included a preoperative CT scan revealing the presence of an omental cake extending to the spleen, the diaphragm coated by cancer that extends to the liver serosa, greater than 2-cm lesions in the suprarenal para-aortic lymph nodes and in the portahepatis, parenchymal liver disease, pulmonary metastases, and enlarged pericardial lymph nodes. Since that time, numerous studies have been reported, some of which support the “Nelson criteria” and others that fail to support these criteria.
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A presurgical serum CA-125 level had been proposed as a means of identifying which patients could not be optimally surgically cytoreduced.[13-16] In the Memorial Sloan-Kettering Cancer Center experience prior to the year 2000, patients whose serum CA-125 values were less than 500 U/mL could be optimally cytoreduced in 75% of cases, whereas those who had CA-125 values over 500 U/mL could not be optimally cytoreduced in 78% of cases.[13] Since the year 2000, the gynecologic oncologists at that institution have employed a more radical approach to the surgical management of ovarian cancer.[17] In their most recently reported experience, the serum CA-125 level no longer reflects their ability to optimally cytoreduce the patient. A similar observation had been made by the Yale investigators.[18]

Because of the failure of either diagnostic imaging or serum CA-125 levels to consistently reflect the likelihood of suboptimally cytoreducing patients, laparoscopy has been utilized, to attempt to identify which patients can be optimally cytoreduced.[19-21] Currently, cytoreduction scores are being evaluated by physicians who are performing laparoscopy on their patients to identify those likely to be optimally cytoreduced. An attempt to use microarray techniques to identify advanced-stage ovarian cancer patients who might be optimally cytoreduced had a predictive accuracy of 72.7%, supporting the hypothesis that optimal surgical cytoreduction is due, at least in part, to biologic characteristics of the cancer.[22] At present, there is no absolute way to identify which patients with advanced-stage ovarian cancer will or will not be able to be optimally cytoreduced at the time of their initial operation.

What the Literature Suggests About Neoadjuvant Chemotherapy

Gynecologic oncologists have broadly accepted the concept that all patients with advanced-stage ovarian cancer must initially be aggressively operated on to optimally surgically cytoreduce the cancer and then receive platinum-based combination chemotherapy. Any change to this approach should only be done under dire circumstances, such as extremely advanced disease in a patient with a very poor performance status or in a situation where change in treatment would significantly improve survival.

The currently available published data suggests that for most series, patients with stage IIIIC disease do as well with neoadjuvant chemotherapy followed by aggressive cytoreductive surgery as they do with conventional treatment. However, it is routine in these retrospective, nonrandomized series that patients with the most advanced disease and the least likelihood to be optimally cytoreduced received neoadjuvant chemotherapy, whereas those with the least advanced disease and best chances to be optimally surgically cytoreduced underwent surgery first. For stage IV disease, there is retrospective evidence that patients do better with neoadjuvant chemotherapy.

Timing and Sequence of Treatment

Timing of surgery following initiation of neoadjuvant chemotherapy is the major variable in the management of women with advanced-stage ovarian cancer. Prospective randomized European trials have used three cycles of neoadjuvant chemotherapy, followed by surgery and postoperative administration of three more cycles of chemotherapy. A Japanese trial is employing four cycles of neoadjuvant chemotherapy, followed by surgery and four more cycles of chemotherapy. At Yale University, we have administered six cycles of chemotherapy, as long as the serum CA-125 levels are declining or normalized, before surgery is performed. As it is routine that some evidence of cancer persists even after six cycles, three additional cycles of the same chemotherapy is recommended following surgery.

Clinical Reports on Neoadjuvant Chemotherapy

More than 30 retrospective reports from institutions around the world are now available regarding the role of neoadjuvant chemotherapy in the management of advanced-stage ovarian cancer. Many of these articles have recently been reviewed.[23] Unfortunately, no published prospective randomized trials are currently available to answer questions about selection of patients, dosage, and number of treatments of neoadjuvant chemotherapy prior to surgery in the management of advanced-stage disease.
Almost all of the published neoadjuvant chemotherapy clinical trials suffer from the same difficulty—the patients described in these trials are not randomized to their treatment regimens. Patients with the most advanced disease routinely received neoadjuvant chemotherapy. Patients most likely to be optimally surgically cytoreduced underwent conventional treatment—ie, cytoreductive surgery followed by adjuvant chemotherapy.

Meta-analysis
Recently, a meta-analysis on neoadjuvant chemotherapy was performed.[24] The meta-analysis included 22 published series of patients, involving 18 different chemotherapy regimens and 13 different chemotherapeutic agents. Unlike the two recently published large Gynecologic Oncology Group (GOG) studies investigating conventional treatment of stage III and IV ovarian cancer, where the chemotherapy dose and duration was the same for all patients, there was no standardization of the chemotherapy regimens, doses, or the duration of neoadjuvant chemotherapy treatment prior to surgery in the reports entered into the meta-analysis.[1,2,24]

The authors of the meta-analysis used a relatively simple but less precise method for this meta-analysis. They pooled the data together, using each study as a data point instead of pooling individual patients together from each study. They then used a simple linear regression analysis instead of a survival analysis. Their pooled analysis may have generated possible leads regarding the role of neoadjuvant chemotherapy in the management of advanced-stage ovarian cancer, but the results were far from definitive. They did recognize that neoadjuvant chemotherapy patients treated with a combined platinum/taxane regimen did better than patients treated with other regimens—a finding consistent with the GOG 111 trial and the Yale data.[18,25]

A subsequent review of neoadjuvant chemotherapy reports in advanced-stage ovarian cancer by the authors who reported the meta-analysis above, classified all of the reported study’s results into one of three categories.[23] The first group reportedly demonstrated inferior survival after neoadjuvant
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chemotherapy compared to survival after primary cytoreductive surgery. The second group showed no difference in survival outcome between neoadjuvant chemotherapy and a less than maximal primary cytoreductive surgical effort. The third category was associated with very favorable survival results for the neoadjuvant chemotherapy–treated patients, but was criticized by the authors for “the generous nature” of the patient inclusion criteria. These authors noted in their conclusion that “additional research is needed to characterize the appropriate proportion of patients in which an attempt at primary surgery should be deferred in favor of initial chemotherapy.”[25]

Yale Studies

A more recent study from Yale University demonstrated that patients treated with neoadjuvant chemotherapy consisting of carboplatin and paclitaxel did significantly better than those treated with carboplatin and cyclophosphamide.[18] This finding was consistent with the GOG 111 study, which revealed that stage IIIC ovarian cancer patients with > 1 cm maximum diameter of residual disease or stage IV patients treated with cisplatin and paclitaxel did statistically better than those treated with cisplatin and cyclophosphamide.[25]

In the most recent Yale neoadjuvant chemotherapy study there was no difference in progression-free or overall survival for patients treated with carboplatin and paclitaxel given in a neoadjuvant chemotherapy regimen for six cycles followed by aggressive cytoreductive surgery or those treated initially with conventional cytoreductive surgery followed by the same combination chemotherapy for six cycles (Figure 1).[18] Approximately 33% of patients in the Yale study who underwent conventional treatment were cytoreduced to no residual disease, whereas 80% of patients who received neoadjuvant chemotherapy first and then underwent surgery were cytoreduced to no residual disease.

The 18-month progression-free survival experienced for the patients receiving carboplatin and paclitaxel in both the neoadjuvant chemotherapy arm and the conventionally treated group was consistent with the intravenous chemotherapy experience reported in the GOG 172 clinical trial.[26] All of the latter patients had stage III disease that was optimally surgically cytoreduced. The 83-month overall survival for the Yale neoadjuvant chemotherapy–treated patients compares favorably with the overall survival of 65.5 months for intraperitoneally treated patients in the GOG 172 clinical trial, especially since the GOG 172 protocol was confined to patients who were optimally cytoreduced to less than 1 cm of residual disease.[18,26] It also compares well to results from Eisenkop et al, who initially optimally cytoreduced 87.7% of stage IIIC patients and reported a 75.8-month median survival.[27]

Stage IV Disease

Survival statistics for stage IV patients treated with neoadjuvant chemotherapy in the Yale series were statistically better for progression-free and overall survival compared to conventionally treated stage IV patients in that series (Figure 2).[18] This observation is not new. Vergote et al reported in 1998 that patients treated with neoadjuvant chemotherapy for stage IV disease did better than conventionally treated patients.[28] The recent Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) stage IV ovarian cancer study reported that patients who were treated in a conventional fashion and were optimally cytoreduced had a 23-month overall survival, whereas those who received neoadjuvant chemotherapy for stage IV disease and then were optimally cytoreduced had a 46-month median duration of survival.[29] In my experience, neoadjuvant chemotherapy must be followed by surgery in order to achieve these excellent results.[5] That surgery should be done by surgeons trained in gynecologic oncology who are willing to make a maximum surgical effort in order to achieve these results.

Intrathoracic Disease

Stage IV patients initially presenting with malignant pleural effusions have a significantly poorer survival even when optimal cytoreductive surgery is performed in the abdomen and pelvis.[2,30] In an effort to determine the presence of intrathoracic disease and possibly to cytoreduce their disease, video-assisted thoracic surgery (VATS) has been evaluated in 21 patients with stage IV ovarian cancer based on the presence of a right-sided malignant pleural effusion.[31] Of these 21 patients, 12 underwent cytoreductive surgery, 3 of whom had intrathoracic cytoreduction performed. Among these 12 patients, 11 had optimal cytoreduction to ≤ 1 cm in the pleural and peritoneal cavities following VATS.

The remaining 9 patients, 8 of whom initially had > 1 cm intrathoracic disease documented by VATS, received neoadjuvant chemotherapy followed by interval surgical cytoreduction. Six of the nine were surgically cytoreduced to no macroscopic residual disease. The remaining three patients were optimally cytoreduced to ≤ 1 cm following neoadjuvant chemotherapy. Survival data were not
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**Impact of Histology**

Patients who received neoadjuvant chemotherapy overwhelmingly had histologically poorly differentiated cancers.[25,26] However, a recent report suggested that neoadjuvant chemotherapy may not be effective in the treatment of low-grade serous cancers.[32] Schmeler et al from M.D. Anderson Cancer Center reported on 25 patients with low-grade serous cancers of the ovary (n = 22) or peritoneum (n = 3) treated in a neoadjuvant fashion with platinum-based chemotherapy. Of these 25 patients, 11 (44%) underwent exploratory laparotomies first to determine surgical cytoreducibility. Only 1 patient had a complete clinical response to the chemotherapy, 21 had stable disease radiologically, and 2 progressed radiologically. Similar discouraging findings were reported from this institution when patients with low-grade serous cancers were treated conventionally. Results included a 5% negative second-look surgery rate and a median progression-free survival of 19 months.[33]

**Advantages of Neoadjuvant Chemotherapy Over Conventional Therapy**

Subjectively, patients who received neoadjuvant chemotherapy prior to surgery appear to be in better physical condition and emotionally better prepared to undergo the surgery.[34] In part this is because successful neoadjuvant chemotherapy will eliminate pleural effusions and ascites, allowing patients to eat better and to return more rapidly to their normal state of health than when they undergo initial radical cancer surgery. In the Yale experience, the operative time was significantly decreased (to 211 minutes) when neoadjuvant chemotherapy was administered followed by surgery than when surgery is done prior to chemotherapy (276 minutes). In addition, blood loss was significantly less with the neoadjuvant approach (546 vs 1,033 mL). Surgical intensive care unit stays were shorter (2 vs 1.6 days), and total hospitalization stays were significantly shorter (5.7 vs 8.5 days).[18]

**Prospective Randomized Trials**

No prospective randomized trials in the United States have evaluated neoadjuvant chemotherapy against conventional treatment for advanced ovarian cancer. One international prospective randomized trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) has completed accrual of patients. The EORTC 55791 trial randomized over 700 women to receive either neoadjuvant chemotherapy for three cycles, followed by cytoreductive surgery and then three additional cycles of chemotherapy, or surgery followed by six cycles of chemotherapy.[35] For the latter arm, there was an option to perform interval cytoreduction following three cycles of chemotherapy if the surgeon declared that it was his or her intent to do so prior to performing the initial surgery. A very similar trial, Chemotherapy or Upfront Surgery (CHORUS), is now accruing patients in a UK study.[35] Over 300 patients have joined this trial, which has a total goal of accruing 550 patients. Finally, the Japanese Clinical Oncology Group is inviting patients to participate in a prospective randomized trial wherein 350 women will be randomized to receive either four cycles of carboplatin and paclitaxel followed by surgery and four additional cycles of treatment, or initial cytoreductive surgery followed by eight cycles of carboplatin and paclitaxel.[36]

**Future of Neoadjuvant Chemotherapy for Advanced Ovarian Cancer**

Preliminary results from the EORTC 55791 study are expected to be available in the fall of 2008 (personal communication). The initially released results will focus on morbidity. Survival data should be available in the spring of 2009. If there is no difference in survival between conventional therapy and neoadjuvant chemotherapy in the EORTC data and the morbidity is improved among women receiving neoadjuvant chemotherapy, neoadjuvant chemotherapy may become an accepted standard technique for the management of patients with advanced-stage ovarian cancer. Indeed, the latter is already true in Ottawa, Canada.[37]

Aletti et al have proposed a treatment strategy for patients with stage IV disease.[38] Neoadjuvant chemotherapy would be offered to patients with multiple hepatic metastases or extensive pleural disease. Patients with a good performance status (American Society of Anesthesiologists [ASA] 1 or 2) would undergo attempted debulking. Those with poor performance status (ASA 3 or 4) would undergo laparoscopy. For the latter, those found to have extensive peritoneal or unresectable disease would receive neoadjuvant chemotherapy, while those who did not would undergo an attempt at primary debulking.

The Southwest Oncology Group recently provided preliminary data on survival for patients believed to be not optimally cytoreducible. These advanced-stage disease patients received neoadjuvant chemotherapy for three cycles and then underwent cytoreductive surgery.[39] Those who were
optimally cytoreduced received intraperitoneal chemotherapy to complete their treatment. The survival data were similar to results seen in patients who underwent surgery followed by chemotherapy in a conventional manner.[39]

Laparoscopic surgery has become a routine part of the management of patients with gynecologic cancers. It is often used by European gynecologic oncologists to determine whether a patient can initially be optimally cytoreduced. Should neoadjuvant chemotherapy become an accepted standard of care, it is possible that among those who achieve a clinical complete response or who have limited and isolated tumor nodules noted on posttreatment CT scans, selected patients will then undergo laparoscopic surgery to remove residual disease as well as reproductive organs that are still in place.

**Unresolved Questions**

The critical question regarding neoadjuvant chemotherapy for the management of advanced-stage ovarian cancer concerns the estimation of surgical cytoreducibility. The survival data, which have been available since 1974, strongly suggest that the best approach to the initial treatment of advanced-stage ovarian cancer is to resect all gross cancer.[40] Estimating cytoreducibility by diagnostic imaging, serum biomarkers, laparoscopic, and molecular biologic techniques has proven to be less than completely reliable. Efforts must be made to identify patients with advanced disease who can be cytoreduced to no gross residual disease, as they benefit the most from this approach. A second question is: How many cycles of chemotherapy should be given prior to performing the surgery? The excellent findings obtained by the Yale group were the result of giving six cycles of chemotherapy (carboplatin and paclitaxel) prior to patients undergoing cytoreductive surgery.[21] The EORTC and CHORUS trials selected three cycles of chemotherapy prior to surgery. The Japanese Clinical Oncology Group trial uses four cycles of chemotherapy prior to surgery.[36]

Finally, and perhaps most significantly, the management of residual disease—which may represent chemoresistant clones of cancer cells—identified at the time of surgery following neoadjuvant chemotherapy will remain an issue. The possibility exists that the cancer that persists after neoadjuvant chemotherapy for advanced-stage ovarian cancer represents ovarian cancer stem cells, which are known to be inherently chemotherapy-resistant.[41] Strategies for treating ovarian cancer stem cells are currently being developed.

**Recommendations**

Medically compromised patients who are physically unable to tolerate aggressive cytoreductive surgery should undergo neoadjuvant chemotherapy first, followed by aggressive cytoreductive surgery if their medical condition improves. Likewise, patients with stage IV ovarian cancer do poorly with conventional therapy, and thus, neoadjuvant chemotherapy should become a standard alternative approach to treating this particular group of women.

All women with stage IIIC disease should be evaluated by a gynecologic oncologist. If the gynecologic oncologist feels the patient can be optimally cytoreduced to no macroscopic residual disease, surgery should be the first step in treatment. If it is expected that macroscopic disease will be left behind, the patient should be offered the choice of either neoadjuvant chemotherapy or conventional therapy.

**References:**


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