Controversies in the Management of Advanced Ovarian Cancer

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Whether advanced ovarian cancer should be treated with neoadjuvant chemotherapy or primary debulking surgery is one of the most debated topics in gynecologic oncology. In their article "Cytoreductive Surgery for Advanced Ovarian Cancer: Quo Vadis?" Schorge and his coauthors provide an excellent review of issues surrounding the management of advanced ovarian cancer. Primary cytoreductive surgery has been the cornerstone of treatment of advanced ovarian cancer. Theoretically, cytoreductive surgery can mediate the adverse metabolic effects of a large tumor burden, decrease chemotherapy resistance, and thereby improve the chances of responding to adjuvant treatment. Survival is predicated on the amount of disease present after cytoreduction. The most important benefit is the inverse relationship between the amount of residual disease and subsequent survival outcome. Although optimal cytoreductive surgery is the most important prognostic factor, optimal cytoreduction cannot be achieved in all patients with advanced ovarian cancer. The achievable rate of optimal cytoreduction for advanced disease varies widely; in addition, there is considerable heterogeneity among definitions of what could be regarded as optimal surgical outcome. Numerous studies have shown that to increase rates of optimal cytoreduction often requires the incorporation of a variety of ablative techniques and extensive upper abdominal procedures.[1] These techniques cannot be applied to all patients irrespective of comorbidity and performance status.

Neoadjuvant chemotherapy (NACT) is sometimes utilized when optimal cytoreduction is not deemed possible, in older patients with multiple comorbidities, and in patients with poor performance status. The theory behind NACT is that it reduces tumor load, which decreases the need for extensive surgery, thereby lowering the perioperative morbidity and increasing the chances of optimal cytoreduction. However, due to lack of reliable evidence, the efficacy of NACT has been repeatedly challenged. The value of debulking after induction chemotherapy has been extensively debated in the past few decades.

The major concern about neoadjuvant chemotherapy in the management of advanced-stage ovarian cancer has been the issue of survival. While most data suggest worse patient outcomes with NACT,[2] a more recent randomized trial by the European Organisation for Research and Treatment of Cancer (EORTC),[3] described in the Schorge et al review, showed similar outcomes for both studied approaches (NACT with interval debulking, or primary debulking). Even though a survey of Society of Gynecologic Oncologists (SGO) members on the use of NACT as primary treatment for ovarian cancer revealed that they treated less than 10% of patients with NACT, 39% of the respondents indicated that they believed women with bulky upper abdominal disease on preoperative imaging would benefit from NACT.[4] The survey also showed that about 20% would perform interval debulking by minimally invasive techniques if there was no gross residual disease after NACT.

A substantial number of SGO members have adapted the use of intraperitoneal (IP) chemotherapy to complete the therapy for women with minimal residual disease after initial NACT and interval debulking. Further studies are needed to validate this approach. The National Cancer Institute of Canada Clinical Trials Group has developed a protocol for a randomized phase II/III study that will examine whether IP platinum-taxane-based chemotherapy benefits women who have received neoadjuvant chemotherapy before optimal surgical debulking.[5] A retrospective review of 44 patients treated with taxane/platinum-based NACT followed by postoperative IP chemotherapy did not show the survival benefit associated with IP chemotherapy after optimal upfront surgery.[6] In this paper, Schorge et al review the published data but do not provide clear guidelines to clinicians as to what the best approach should be. In the absence of data from well-designed, well-conducted phase III randomized trials, it is difficult to formulate such guidelines, and a more personalized approach to each patient may be necessary. There is no universally applicable clinical model that
can predict which patients will undergo optimal cytoreduction. Abdomino-pelvic computed tomography along with CA 125 testing is used by many gynecologic oncologists to predict resectability, but both studies have been shown to have limitations. Bristow et al developed a predictive index that was able to correctly predict surgical outcome (optimal [< 1 cm] vs suboptimal residual disease status).[7] The specificity for the ability to identify patients who would undergo optimal debulking was 80%. The authors do agree that a laparoscopy—and in certain situations, exploratory laparotomy—provides certain advantages as a selection tool. Furthermore, surgical skills make a difference in the setting of more advanced disease and may result in higher rates of complete resection that may translate to better overall outcomes. A multicenter, randomized controlled trial is needed to resolve some of the controversies surrounding this topic. This trial should be designed to address critical issues, such as the definition of uniform selection criterion that can consistently identify patients with surgically unresectable disease, and it should also look into the complex interaction between patient-related characteristics, tumor biology, and operative expertise.

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References:

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