



Extra cycles of neoadjuvant chemotherapy before interval surgery for ovarian cancer: the more the merrier or too much of a good thing?

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Four randomized trials demonstrated that patients with advanced ovarian cancer assigned to neoadjuvant chemotherapy followed by interval surgery had similar survival to patients randomized to primary surgery followed by adjuvant chemotherapy.¹ Based on the protocols of these studies, which limited the number of chemotherapy cycles prior to interval surgery to three or four, the American Society of Clinical Oncology favors no more than four cycles prior to surgery.² However, in clinical practice patients sometimes receive more than four cycles of neoadjuvant chemotherapy and observational studies examining timing of interval surgery in this setting have yielded contradictory results.

Initial observational studies predating randomized neoadjuvant chemotherapy trials found that more cycles of neoadjuvant chemotherapy were associated with a survival decrement in ovarian cancer. A 2006 meta-analysis of observational studies concluded that each additional cycle was associated with a 4.1-month decrease in median survival,³ and another retrospective study found that receiving more than four cycles was associated with almost 2.3 times worse odds of survival.⁴ These and other observational studies are challenging to interpret because they do not account for tumor biology or disease burden, which may confound the association between the number of neoadjuvant chemotherapy cycles and survival. Patients with a more aggressive phenotype may require more cycles of neoadjuvant chemotherapy to achieve a response. Such patients are likely to have a worse prognosis than those who achieve a good response after three or four cycles, even if the number of cycles administered before surgery has no causal effect on survival. Observational studies that compare patients who received additional chemotherapy after three or four cycles because they had a poor initial response with those who had a robust response after three or four cycles and proceeded to surgery cannot provide unbiased estimates of the effect of those additional cycles if they ignore the biological differences between these cancers.

The Lead Article this month is an observational study investigating the association between the number of neoadjuvant chemotherapy cycles and oncologic outcomes among patients with advanced ovarian cancer. Bétrian and colleagues investigate a cohort of patients who received neoadjuvant chemotherapy followed by interval debulking among four institutions in Europe.⁵ All patients were assessed after three or four cycles and those with stable disease on imaging or at laparoscopic assessment received three additional cycles. In the multivariable analysis, this study includes both residual disease after interval surgery and the chemotherapy response score as covariates. They found that, among 365 patients, the number of cycles of neoadjuvant chemotherapy was not associated with overall survival after accounting for chemotherapy response score and residual disease. On the other hand, a poor histologic response was associated with residual disease, early relapses and worse survival. The incorporation of variables related to tumor biology is a strength of this investigation; however, the results are limited by selection bias (exclusion of patients with residual disease >2.5 cm) and the non-randomized study design.

Although well-designed observational studies such as this one suggest that individualizing surgical timing after neoadjuvant chemotherapy based on patient and tumor characteristics may be safe, a definitive answer to this question requires a randomized trial. Fortunately, such a trial is already ongoing—the CHRONO study⁶ is a prospective randomized phase III trial comparing progression-free survival among patients randomized to three cycles of neoadjuvant chemotherapy with those randomized to six cycles prior to interval surgery.

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