Early-Stage Ovarian Cancer: To Treat or Not To Treat

Robert C. Young

Approximately one-third of patients with epithelial ovarian cancer present with localized disease confined to the ovaries or pelvis (International Federation of Gynecology and Obstetrics [FIGO] stages I and II). Although their long-term prognosis is better (10-year survival = 50%–70%) than that of patients with advanced ovarian cancer (10-year survival = 15%–25%), approximately 50% of women with early-stage disease eventually relapse and succumb to their disease (1). These suboptimal survival results have led to major efforts to identify prognostic factors, improve surgical staging, and develop adjuvant therapies that could improve patient outcome. Earlier trials have been hampered by small size and limited statistical power and have not established a clear survival benefit for adjuvant treatment. Total abdominal irradiation and intraperitoneal radioisotopes, commonly used years ago, have generally been replaced by platinum-based adjuvant chemotherapy regimens; however, large, prospective randomized trials of adjuvant treatments have been sorely needed.

The two prospective trials and the combined analysis of the two trials published in this issue of the Journal add important information on adjuvant chemotherapy but leave some critical issues unresolved (2–4). The International Collaborative Ovarian Neoplasm (ICON1) and the Adjuvant ChemoTherapy In Ovarian Neoplasm (ACTION) trials, which were carried out over almost a decade, were originally conceived to be much larger trials, with 2000 and 1000 patients, respectively. Both trials had similar randomization procedures, to either platinum-based adjuvant chemotherapy immediately following surgery or no adjuvant chemotherapy until clinically indicated. Both trials allowed considerable flexibility about the chemotherapy regimens used in their studies as long as a platinum drug was included. Patient inclusion criteria were, however, different in the two trials. The ICON1 trial included all patients with early stages, grades, and histologic cell types and used an unusual entry criterion that allowed entry into the trial “if, in the opinion of the responsible clinician, it was uncertain whether the patients would benefit from immediate adjuvant chemotherapy.” Total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were recommended but not required for patient entry, although all visible tumor had to be removed. The ACTION trial used more restrictive and traditional entry criteria: all patients with FIGO stage Ia and Ib, grade II–III; all stages of Ic and IIa; and all stages of I–Iia with clear-cell carcinomas of the ovary were eligible for entry into the study. Strict guidelines for comprehensive surgical staging and tumor typing and grading were required.

Despite considerable differences between the two trials, the outcomes were remarkably similar. The analysis of the combined trials showed better overall survival (OS) for patients in the adjuvant chemotherapy arm than for patients in the no-adjuvant-chemotherapy arm, with a difference in OS of 8% in favor of chemotherapy (82% versus 74%, respectively; \( P = .008 \)). Recurrence-free survival (RFS) was also better for patients in the adjuvant chemotherapy arm than for patients in the no-adjuvant-chemotherapy arm (76% versus 65%, respectively; \( P = .001 \)). Only when the ACTION trial was analyzed separately was a survival difference between the trial arms not seen (\( P = .10 \)).

The combined results of the two trials, which comprised 925 patients, would seem to be definitive proof of the benefit of platinum-based adjuvant chemotherapy for all patients with early-stage ovarian cancer. Unfortunately they are not. The ICON1 trial, with its broad patient entry criteria, included good-prognosis patients (i.e., 32% of patients had well-differentiated histology), who are normally excluded from such trials, and likely included poor-prognosis patients who may have had occult stage III disease; approximately 25% of patients with incompletely staged ovarian cancer harbor more advanced disease (5). Although these patient inclusions may cancel each other out and make the two trials appear similar, they do not necessarily enable the clinician to know which patients require treatment. In the ACTION trial, where comprehensive surgical staging was required, the one-third of the patients who had optimal surgical staging retrospectively showed neither an OS nor a RFS benefit from adjuvant chemotherapy. This lack of survival benefit suggests that platinum-based adjuvant chemotherapy primarily affects patients who may have been incompletely staged from the outset. Certainly, patients with high-risk, early-stage epithelial ovarian cancer who are either incompletely staged or for whom data is incomplete or unavailable should receive platinum-based adjuvant chemotherapy. However, previous studies with long-term survival data have shown that many patients with early-stage ovarian cancer have already been cured with surgery alone (6,7).

The goal, therefore, should be to identify patients who can be spared unnecessary adjuvant chemotherapy. Here, however, both trials fall short of the ideal. The ICON1 trial included patients who were excluded from the ACTION trial and who are excluded from most other early-stage ovarian cancer trials (6–9). In the ICON1 trial, no data were presented to suggest that the low-risk subset of patients—patients with well-differentiated histology, stage Ia and Ib—benefit from adjuvant chemotherapy. Although the retrospective subset analysis of the ACTION trial suggests that accurate surgical staging identifies patients who do not require adjuvant chemotherapy, only one-third of the patients in the trial could be optimally staged. This limited staging success indicates that, even in the best of surgical hands, optimal staging can be problematic. Furthermore, other trials where optimal staging has been used have shown modest survival benefit from adjuvant chemotherapy over other treatment modalities such as phosphorus 32 (6,7,10). The planned trial by the European Organisation for Research and Treatment of Cancer (EORTC) collaborators, which will leave optimally staged patients off treatment and attempt to restage patients who were initially incompletely staged, will be challenging to accomplish.
but will provide helpful information on which, if any, of these patients benefit from adjuvant chemotherapy.

Although the approach of the ICON1 trial could be lauded as a “real world” approach, it is difficult to see how their patient entry criteria, using clinician opinion about whether a patient needs adjuvant chemotherapy, can be consistently or uniformly used by clinicians. Likewise, the real world approach overtreats a large number of patients in an effort to benefit a few. In addition, the ACTION and ICON1 trials assume that the various chemotherapy regimens used in their studies are interchangeable and equally effective. Certainly in many solid tumors and, indeed, in advanced ovarian cancer, this is not the case (11). In contrast, trials by the Gynecologic Oncology Group (GOG) have focused on different chemotherapy regimens and treatment durations. To complicate comparisons, in recent years the GOG has not included an observation arm (i.e., no-adjuvant-chemotherapy arm) in trials of high-risk patients. Therefore, the focus of subsequent trials must be on identifying patients who do not require additional therapy, while also seeking to improve therapy in patients who do. Selecting only high-risk patients for additional treatment can narrow the use of chemotherapy, and this approach should be used until such time as a randomized trial can demonstrate that good-prognosis, early-stage patients benefit from such therapy. A high priority for subsequent studies will be to use molecular markers, gene expression and microarray profiles (12), DNA ploidy (8), or serum protein patterns (13) to further separate good- from poor-prognosis early-stage disease. We also need better adjuvant therapies for the discouraging subset of early-stage ovarian cancer patients who, in spite of minimal disease and optimal therapy, still succumb to their disease.

REFERENCES


