CORRESPONDENCE

Re: Adjuvant Chemotherapy in Patients With Early-Stage Ovarian Cancer

The authors of the two largest randomized trials (1,2) addressing the use of adjuvant chemotherapy in early-stage ovarian cancer are to be congratulated for seeing them through to publication after 12 years. The addition of two earlier trials of adjuvant chemotherapy in early-stage ovarian cancer in the meta-analysis presented in the combined analysis of the two trials (3) only reinforced the authors’ most important conclusion that, in early-stage disease, the small number of events limits statistical and clinical interpretation. The demonstration of a modest benefit of adjuvant chemotherapy for overall survival (8% at 5 years) and recurrence-free survival (11% at 5 years), based on 245 events, is important enough to influence clinical decision making (3).

However, uncertainties remain. First, the chemotherapy regimens used for ovarian cancer have changed in the past 12 years, with modifications in dose intensity, development of new drug analogs, and the incorporation of additional agents into the management of advanced disease. Extrapolation to early-stage disease may be problematic, not least because the additional late toxicity from drug combinations is a greater factor in stage I and II disease where more than 70% of patients survive 5 years (3).

Second, there have been developments in histopathologic assessment. Borderline tumors, a category of tumors that was excluded from both trials (1,2), are subject to considerable interobserver variation (4), and clear-cell carcinomas, which make up 15%–20% of early-stage disease, have a poorer prognosis and respond less well to chemotherapy than other epithelial types. Unfortunately, neither of these two trials used centralized histopathologic review of the diagnostic category or grade of tumors.

Finally, the text of the three articles (1–3) suggests differing views on the issue of surgical staging between the two research groups, and it is widely recognized that there are divergent opinions both in Europe and the United States on the optimal surgical approach to staging in ovarian cancer. Interestingly, there is evidence suggesting variation in overall survival associated with the expertise of the gynecologist performing the surgical procedure and, in early-stage ovarian cancer, a substantial proportion of patients are operated on by nonspecialist physicians (1,5). There was little difference between the minimum requirements for surgical staging in both the International Collaborative Ovarian Neoplasm 1 (ICON1) and the Adjuvant Chemotherapy In Ovarian Neoplasm (ACTION) trials; both required clearance of all macroscopic disease. However, in the ICON1 trial, surgical staging data were not recorded, whereas the physicians participating in the ACTION trial were strongly advised to consider performing more comprehensive staging.

A post hoc subgroup analysis of optimally staged patients, which was based on only one-third (151 case patients, 18 events) of the ACTION trial’s patients, led the authors of that trial to conclude that adjuvant chemotherapy may not benefit optimally staged patients. The practical question is whether restaging of non-optimally staged patients, which may increase the stage category in 20% of patients, is worth the effort and risk. The expected gain in survival is likely to be small, and it may be argued that the benefits of cytotoxic chemotherapy have improved survival to the extent that the differences between small macroscopic and microscopic disease are overcome by chemotherapy.

Oncologists should, therefore, accept the findings of these two trials (1,2) and the conclusions of the meta-analysis (3) as the best evidence currently available for the benefit of adjuvant chemotherapy and adopt it, with the exception of stage 1a and b grade 1 tumors, as standard-of-care for early-stage ovarian cancer (6). At a minimum, the standard chemotherapy regimen should contain carboplatin at an area under the curve dose level of 6 mg · min/mL, which has been shown to have acceptable morbidity (3). Furthermore, pragmatic surgical staging guidelines, which are achievable in 80% of ovarian cancer cases, should be agreed on internationally, and mechanisms should be devised to ensure that tumor tissue can be stored and exchanged on a global basis for analysis at both the morphologic and molecular level.

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RESPONSE

Dr. Green states that the change in chemotherapy regimens used for ovarian cancer over the past 12 years creates problems in interpreting the results of the International Collaborative Ovarian Neoplasm 1 (ICON1) (1) and Adjuvant Chemotherapy In Ovarian Neoplasm (ACTION) (2) trials. We agree that it would be difficult to interpret these results if no effect of chemotherapy had been observed; however, because overall survival was improved and the platinum-based chemotherapy used in these...
trials remains the mainstay of treatment, the findings of the two trials remain relevant and provide important evidence for determining the best treatment for women with early-stage ovarian cancer. Furthermore, the fact that the majority of patients in both trials (57%) received single-agent carboplatin makes this chemotherapy regimen the recommended treatment. We do agree that our findings should not be extrapolated to other chemotherapy regimens. Results of clinical trials with evidence of more effective chemotherapy regimens or more effective new drug analogs than single-agent carboplatin are not available in the early disease setting.

The criticism that centralized pathologic review was not performed in the ICON1 and ACTION trials has no impact on their findings. Centralized histopathologic review does not take place in the real world, and these were real world trials. Randomization within large trials ensures that potential misclassification is equally distributed between treatment arms. Moreover, there was no evidence from the planned subgroup analyses of the combined trials (3) that any tumor subtypes, including clear-cell tumors, responded differently to treatment than other tumor types.

It is true that there were differing views between the ICON1 (1) and the ACTION (2) investigators on whether patients who are optimally surgically staged benefit from adjuvant chemotherapy. The authors of the ACTION trial chose to draw conclusions from a small, unplanned subgroup analysis of 151 patients with optimal disease staging (one-third of the patients in the trial) who contributed only 18 events to the survival analysis. Although the hazard ratio for the risk of death in this group suggests a 24% reduction in the relevant risk of death in favor of no chemotherapy (using the Mantel–Haenszel version of the log-rank test) (4), the 95% confidence intervals [CIs] are wide (95% CI = 0.51 to 3.15), ranging from a twofold reduction in the relative risk of death with adjuvant chemotherapy to a twofold increase in the relative risk of death with adjuvant chemotherapy.

The suggestion that the findings of the ICON1 (1) and ACTION (2) trials should not be applied to patients with stage Ia or Ib ovarian cancer is not founded on evidence from those trials, which included 430 stage Ia and Ib patients (47%). In addition, there was no evidence of heterogeneity of the treatment effect according to disease stage (shown in Fig. 3 of the combined analysis (3)); the test for interaction was not statistically significant (P = .73). Therefore, all patients are likely to benefit from adjuvant chemotherapy by the same relative amount, and the findings apply equally to all patients with early-stage ovarian cancer.

This fact still allows for the interpretation that, for patients with a good prognosis (i.e., a 90%–95% survival rate), the relative benefit of adjuvant chemotherapy may translate into only a small absolute benefit in survival of 1%–2%. In these circumstances, some doctors and patients may not believe that adjuvant chemotherapy is worthwhile. Hence, the decision whether to give and/or receive adjuvant chemotherapy must be made according to the expected risks and benefits for an individual patient—a clinical judgment similar to the one made when deciding to conserve an ovary in a young woman with ovarian cancer who wishes to have children. Therefore, the conclusion that all patients with early-stage disease should be considered for adjuvant chemotherapy stands.

DAVID GUTHRIE ON BEHALF OF THE ICON1 COLLABORATORS

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We thank Dr. Green for his compliments regarding the publication of the European Organisation for Research and Treatment of Cancer (EORTC)–Adjuvant Chemotherapy In Ovarian Neoplasm (ACTION) trial (1). Nevertheless, there are a number of comments with which we disagree.

Dr. Green supports the notion that the benefit of adjuvant chemotherapy is important enough to influence clinical decision making based on the overall and recurrence-free survival results of the combined analysis of the ACTION and International Collaborative Ovarian Neoplasm 1 (ICON1) trials (2). We concur with that statement; however, it is crucial in any extrapolation of research findings to the general population to appreciate the features of the study population. We have argued that the vast majority of patients in the combined analysis would have been non-optimally staged, thus defining this population as a mixed group of patients that has an appreciable portion of patients with undetected residual disease in the abdominal cavity (3). Therefore, the patient population in both ICON1 (4) and the combined analyses (2) might be considered as patients with “supposed” early-stage ovarian cancer. Supposed early-stage ovarian cancer is clearly different from “proven” early-stage ovarian cancer on the basis of comprehensive surgical staging.

Variability in the pathologic assessment of ovarian cancer is predominantly in distinguishing the difference between borderline and grade I tumors (5). ICON1, which allowed all early-stage ovarian cancer patients to be included, comprised 32% of well-differentiated (i.e., grade I) tumors (4). Therefore, the risk of including borderline ovarian tumors in that study may have been substantial. In contrast, the ACTION trial (1), which allowed only medium- to high-risk early-stage ovarian cancer patients to be
included, and that comprised only 12% of well-differentiated tumors, made the risk of including borderline tumors much smaller.

Another comment in Dr. Green’s correspondence is that there are different opinions about optimal surgical staging in Europe and the United States. The EORTC clearly defined its staging guidelines in the early 1990s (6), and they are virtually identical to those of the United States-based Gynecologic Oncology Group (GOG) (7). Dr. Green also commented that there was little difference between the minimum requirements for surgical staging in both the ACTION (1) and ICON1 (4) trials. On the contrary, there was a large difference in the requirements for surgical staging between the two trials. In the ACTION trial, the necessary surgical staging steps were provided in the protocol, and optimal surgical staging was strongly recommended; surgical performance was also comprehensively monitored and analyzed. In the ICON1 trial, surgical staging was not emphasized, not defined, and not even monitored. Therefore, it would be difficult to describe the ICON1 patient population as true early-stage ovarian cancer patients. This notion is supported by a comparison of all ICON1 patients and non-optimally staged ACTION patients in the observation arms (Fig. 1) in which the overall survival curves are almost identical, even though the ICON1 trial included low-risk patients (i.e., stage Ia, Ib, grade I) in 15% of their study population and the ACTION trial did not. These factors strongly suggest that the ICON1 patients should be regarded as predominantly non-optimally staged, limiting the extrapolation of their results and thus, that of the combined analysis (2), to other patient populations.

Dr. Green also commented on the number of events (i.e., 18 deaths) in the optimally staged patients of the ACTION trial (1) as a basis for the conclusion that chemotherapy may not benefit this category of patients. That conclusion was, however, also based on the findings in the non-optimally staged patients (60 events); exactly the same differences in recurrence-free survival between the optimally staged and non-optimally staged patients (28 and 84 events, respectively) were observed. Furthermore, Dr. Green states that the expected gain in survival in the case of optimal surgical staging is likely to be small; however, exactly the same issue can be argued for the case of adjuvant chemotherapy.

Finally, Dr. Green suggested that pragmatic surgical staging guidelines, which are achievable in 80% of ovarian cancer cases, need to be agreed on internationally. This statement seems hard to defend because accurate surgical staging should be based on knowledge of tumor spread and tumor behavior and not on the feasibility of the procedure.

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