Another Confirmation of the Inactivity of Topotecan in Ovarian Cancer

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One decade ago, in an editorial in the Journal (1), I challenged investigators who were interested in improving outcomes to continue conducting multiple trials that addressed similar questions in the treatment of advanced ovarian carcinoma except when the purpose of such studies was to confirm possible practice-changing new treatment strategies. A negative report that appears in this issue (2) is the fifth study to investigate the addition of topotecan to the platinum and taxane backbone, the current standard of care for ovarian cancer that was confirmed here a decade ago (3). The authors even include a table in the article that demonstrates the accrual of 4451 patients to explore various permutations of the question: Does the addition of topotecan to a platinum and taxane backbone improve outcomes in patients with advanced ovarian carcinoma? The answer is a resounding “no” whether topotecan is used in a triplet (4), as part of a sequential doublet (2,5), or as consolidation (6,7).

In the recently published trial by the Gynecologic Cancer Intergroup (5), 4321 ovarian cancer patients were accrued internationally from the United States, United Kingdom, Italy, Australia, and New Zealand. This five-arm study (GOG182/ICON5) explored the addition of topotecan, gemcitabine, or liposomal doxorubicin to the platinum and taxane backbone. None of the new agents improved any outcome measure, and each was more toxic in some fashion than the backbone alone. The accrual spanned the years 2001–2004. The current study (2) was developed during the same time period and accrued 819 patients from Canada, Spain, and several countries from the European Organization for Research and Treatment of Cancer between 2001 and 2005.

Ideally, the investigators from each of the countries above could have cooperated to address the same questions, and perhaps to answer them more quickly and with fewer total patients. It may be that the groups who designed these trials were each unaware of what the other was planning, but frequently, it is only after the protocol is written and patients have been accrued that different groups become aware that they are doing similar studies. Three other studies that added topotecan to the platinum and taxane backbone were simultaneously in the planning or early execution stage when the two international trials above were being planned. In fact, the largest of these trials, which was performed by a German and French consortium, Arbeitsgemeinschaft Gynaekologische Onkologie Studeingruppe Ovarialkarzinom—Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (AGO-GINECO), actively accrued patients between 1999 and 2002 (7). Had the investigators who planned this current trial (2) and the Gynecologic Cancer Intergroup trial (5) had knowledge of early outcomes from the AGO-GINECO studies, they may have deferred initiation of the current trial and at least one arm of the Intergroup trial.

Nevertheless, it takes time for international collaborations to mature, and collaboration can be further complicated by different rules from regulatory agencies in different regions or the lack of agreement from pharmaceutical sponsors in different countries, especially when some agents may be cosponsored by two pharmaceutical companies in different regions. When this current trial was initiated, it seemed reasonable to explore topotecan combined with cisplatin rather than carboplatin (as in the intergroup study) or the use of 5-day topotecan at a lower dose (0.75 mg/m²) as opposed to a more standard dose of topotecan (1.25 mg/m² for 3 days as in the intergroup study). In addition, the sequence of drug administration had been suggested to be important in early trials of topotecan (8), and it differed in this trial (platinum followed by topotecan) as compared with the intergroup study, which used the alternate sequence (topotecan followed by platinum). In the end, neither the dose, sequence, nor platinum compound made any difference.

Conservatively, there are some 150 new compounds in various stages of clinical development that could be evaluated in the treatment of ovarian cancer. Most are targeted therapies aimed at transmembrane signals because cytotoxic agents have become “less interesting.” Precious patient resources are needed to address which of these agents, if any, will improve the therapeutic envelope for advanced ovarian cancer. Clearly, the lack of any benefit from adding topotecan, gemcitabine, or pegylated liposomal doxorubicin to the platinum/taxane backbone in the intergroup trial (5) has signaled the need to try some new approaches.

The most recent attempt to improve outcome has incorporated bevacizumab into primary therapy, again by adding it to the platinum and taxane backbone. The three-arm trial in the United States, GOG 218 (9), has enrolled 1873 patients and was recently reported at the American Society of Clinical Oncology (ASCO). Though sponsored by the Gynecologic Oncology Group (GOG), this was an industry-funded trial (Genentech), and the desire to obtain an answer more quickly may explain the midcourse change of the primary endpoint from overall survival to progression-free survival (PFS). In this trial, the carboplatin and paclitaxel backbone alone was compared with carboplatin and paclitaxel with bevacizumab (cycles 2–5) with or without 1 year of bevacizumab monotherapy as consolidation following the cytotoxic therapy. There was a statistically significant benefit in PFS in the arm that used consolidation therapy but not in the arm in which bevacizumab was only provided during cytotoxic therapy. Whether this positive effect on PFS will translate into a benefit in overall survival awaits follow-up. When Dr Elizabeth
Eisenhauer discussed this trial at ASCO, she pointed out that the correlation between overall survival and PFS is less linear when targeted therapies are added to cytotoxic agents than when cytotoxic agents are combined and that PFS may overestimate the survival benefit. Finally, because the current cost of bevacizumab is substantial, the pharmacoeconomics of the triplet therapy with a year of consolidation may be beyond the resources of many patients or health delivery systems, especially when the benefit in terms of life-years saved is unknown. Thus, this may or may not become a practice-changing trial depending on outcomes with longer follow-up.

A second study (ICON7) was sponsored by the Medical Research Council in Great Britain but, again, funded by industry (Roche): it was a two-arm trial designed exactly like the GOG 218 trial except that it used bevacizumab doses that were half those used in GOG 218 and did not include the arm that provided bevacizumab only with cytotoxic therapy. This trial accrued 1528 patients from many countries outside the United States that have had substantial prior experience with ovarian cancer clinical trials: it included AGO (Germany), the Australia New Zealand Gynaecological Oncology Group (ANZGOG), Grupo de Investigación de Cáncer de Ovario (GEICO: Spain), GINECO (France), NCIC (Canada), and the Nordic Society of Gynaecological Oncology (NSGO: Scandinavia). Unfortunately, we know little of the results yet, possibly because all information is proprietary, except a self-laudatory press release on the Roche Pharmaceuticals website.

Hopefully, longer follow-up of these two trials will allow the clinical trial community to either accept or reject this new three-drug regimen as practice changing. If the results of the Medical Research Council–sponsored study are similar to those of the GOG study and both studies are positive for the overall survival endpoint, then the cost savings with smaller doses of bevacizumab would be substantial. A total of 3300 patients have participated in these two trials, fewer than the 4400 patients in the five trials of topotecan that confirmed its inactivity. The limited and precious pool of patients that all clinical investigators call upon to participate in clinical research studies could better benefit from worldwide coordination of cancer clinical trials than has been the standard of trial development in isolation.

The Gynecologic Cancer Intergroup was formed in the late 1990s, now has membership from 20 cooperative groups (see www.gcig.igcs.org), and currently acts to help coordinate clinical trials in gynecologic cancer across the many nationally based organizations of clinical trialists. In the United States, an outgrowth of this coordinating body is the National Cancer Institute–sponsored Gynecologic Cancer Steering Committee, which is charged with oversight of the design and prioritization of phase III studies funded by the National Cancer Institute. The Institute of Medicine, in its recent report on the National Cancer Clinical Trials System (see www.iom.edu/ncicancertrials), proposed efforts to improve the speed and efficiency of the cancer clinical trials program by improved prioritization and completion of high-priority studies. International collaboration and oversight should be embraced by all of us who participate in clinical trials lest we fail our patients.

References

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