Treatment of Ovarian Cancer With Intraperitoneal Platinum: Heating Up the Debate

TO THE EDITOR:

In their recent article in *Journal of Clinical Oncology*, Walker et al.\(^1\) reported the efficacy and toxicity profile of bevacizumab with intravenous (IV) versus intraperitoneal (IP) chemotherapy for newly diagnosed advanced ovarian cancer in a large intergroup phase III trial (Gynecologic Oncology Group [GOG] 252 trial). Although we appreciate their findings, we believe that the interpretation of the results raises a few important issues for the authors to clarify.

First, GOG-252 confirms that, for patients with advanced ovarian cancer, complete macroscopic debulking represents their best chance of long-term survival. It is a deep-rooted belief among the medical community that when patients with ovarian cancer are treated by gynecologic oncologists in specialized centers where advanced surgical strategies are performed, both resection rate and prognosis are demonstrably improved.\(^2\) Given the large number of centers (n = 213) and the relatively long accrual time period (28 months) needed to conduct GOG-252, it is unclear whether participant centers were high-volume institutions with expertise in gynecologic oncology. Can the authors comment regarding whether institutional patient accrual volume was associated with survival and/or completeness of debulking (eg, accrual per year, forest plot for survival, and complete resection rate per site)? For a better understanding of this issue, more detailed information on surgical procedure characteristics would be appreciated (eg, bowel, diaphragm, or spleen resection; blood loss; duration of surgery; surgical complications; and time between surgery and start of adjuvant therapy).

Second, some adverse events were discussed by the authors, but little to no information is available on renal dysfunction and catheter-related events, both of which posed a problem in GOG-172.\(^3\) Therefore, we would suggest that the authors report in more detail the observed toxicity rates in this trial.

Third, it is our premise that ovarian cancer, particularly stage IV disease, is a systemic disease, and thus, systemic chemotherapy—of which platinum remains to this day the unquestioned backbone—should be offered to these women. However, the purpose of IP administration is to minimize systemic exposure and associated toxicity.\(^4\) As such, the failure to offer IV platinum therapy to participants with stage IV disease in two of three arms when substantial data exist to support its use is,\(^5\) in our opinion, a serious therapeutic omission and a first in a large phase III trial of first-line treatment of ovarian cancer. The exploratory data by Walker et al.\(^1\) argue strongly in favor of a therapeutic benefit for IV over IP platinum in patients with suboptimally resected stage III and stage IV disease because a clinically relevant difference in median overall survival time was observed (55.5 v 50.5 v 43.6 months for IV carboplatin, IP carboplatin, and IP cisplatin, respectively; n = 178). We maintain that patients with stage IV disease should never have been included in the trial in the first place. Nevertheless, we would like to know whether there actually was a difference in survival between patients who received IV platinum (n = 24) and those who received IP platinum (n = 68) in the subgroup with stage IV disease.

Before GOG-252, three large intergroup phase III studies had demonstrated the favorable impact of IP over IV administration of chemotherapy after debulking surgery,\(^4,6,7\) although differences in dose-intensity and schedule of administration between arms confounded interpretation of the IP approach. However, we are doubtful whether the resoundingly negative GOG-252 trial will be enough to solve this three-decade oncologic conundrum. Until more data are available, it is reasonable to conclude that the most convincing evidence to date for IP drug delivery was provided by van Driel et al.\(^8\) Besides the addition of hyperthermia, major differences in the trial by van Driel et al.\(^8\) compared with the present GOG-252 trial, are the timing of surgery (interval v up-front debulking, respectively) and the timing of chemotherapy instillation (intraoperatively v postoperatively, respectively). Because IP chemotherapy was administered postoperatively in GOG-252, we may assume that the formation of peritoneal adhesions blocked free flow and, thus, uniform access of the chemotherapy into the peritoneal cavity.\(^9\)

In conclusion, GOG-252 proves the large-scale feasibility of IP therapy in the adjuvant treatment of ovarian cancer. However, the trial also demonstrates that although IP platinum-based therapy has a similar efficacy to current IV treatment protocols, it requires more interventions (eg, catheter placement and removal), is somewhat less tolerable for the patient, and does not result in less systemic toxicity. In addition, these results are yet another
argument in favor of centralized expert referral for ovarian cancer surgery. Finally, we would argue that further research on IP therapy in ovarian cancer should focus first on the addition of novel IP treatments (eg, immunotherapy, antibody-drug conjugates, or prolonged delivery platforms) to the standard of IV platinum-based therapy, rather than serve as its replacement.

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