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Editorial

Intraperitoneal chemotherapy for women with advanced epithelial ovarian carcinoma

In this issue of *Gynecologic Oncology*, Dr. Joan Walker and her colleagues report the Gynecologic Oncology Group (GOG) experience with intraperitoneal (IP) catheters in GOG 172, a phase III randomized trial comparing intravenous (IV) chemotherapy to a combination of IV and IP chemotherapy among with optimally debulked stage III ovarian cancer [1]. The results for overall survival, the primary endpoint of the trial, have recently been reported by Dr. Deborah Armstrong and her colleagues from the GOG in the *New England Journal of Medicine* [2]. GOG 172 is the third large randomized phase III trial sponsored by the NCI to demonstrate a clinically significant improvement in survival associated with a combined IV/IP approach among women with advanced ovarian cancer [3,4].

The results of these three studies are consistent with those of several smaller randomized trials comparing IV administration of chemotherapy to a combined IV/IP administration. An additional trial compared IP consolidation treatment to no further therapy among women with advanced ovarian cancer without evidence of disease after primary surgery and chemotherapy [5]. Across all these studies, the improvement in overall survival associated with IP administration was 12 months, while the most recent study, GOG 172, showed a 17-month improvement in overall survival. This improvement in overall survival is comparable to that observed with the introduction of platinums and of taxanes into the treatment of women with advanced epithelial ovarian cancer. Although IP administration generally appears to be associated with an increase in toxicity compared to IV administration, that increase in toxicity appears to be relatively short-term and manageable.

Based on these combined results, the National Cancer Institute has issued a Clinical Announcement recommending that women with stage III ovarian cancer who undergo optimal surgical cytoreduction be considered for IP chemotherapy [6]. NCI considers a Clinical Announcement when a clinical trial or trials have identified an intervention which substantially improves the survival outcome for a significant number of people with reasonable certainty and when that intervention is available to the general public. In accordance with NCI guidelines, the data on IP chemotherapy in ovarian cancer were first reviewed by a panel of independent experts, including gynecologic oncologists, medical oncologists, biostatisticians, and patient advocates, jointly nominated by the Clinical Trials Cooperative Groups conducting the largest trials, namely the GOG, the Southwestern Oncology Group, the European Organization for Research and Treatment of Cancer Gynaecological Cancer Group, and the NCI. After review of the data, the panel recommended to the director of the NCI that such a Clinical Announcement be issued. The text of the proposed Clinical Announcement was then reviewed by the panel, as well as the United States Food and Drug Administration and the Office of the Director, National Institutes of Health.

The purpose of this Clinical Announcement is to disseminate this important information widely to physicians and patients. We recognize that there are many barriers to overcome. First, optimal treatment of advanced ovarian cancer requires coordinated multidisciplinary care. Optimal surgical staging and cytoreduction to minimal or no gross residual disease remain the first step, followed by timely administration of platinum- and taxane-based chemotherapy. In many cases, women with ovarian cancer do not have access to gynecologic oncologists or surgical teams with expertise in the surgical management of women with ovarian cancer. The rate of optimal surgical debulking between centers can vary dramatically from 20 to 80% [7]. Second, up to this point, IP chemotherapy for women with ovarian cancer has primarily been restricted to clinical trials. Many gynecologic surgeons and surgical oncologists do not have experience with the placement of IP catheters. Third, many gynecologic oncologists, medical oncologists, and oncology nurses have not had recent experience with the IP administration of chemotherapy. Also, IP administration of chemotherapy is an old idea, which many clinicians appear to view with skepticism. IP therapy lacks the excitement generated by new targeted agents, not to mention the impressive resources which pharmaceutical companies can marshall to promote the introduction of new agents. Finally, the precise reasons IP therapy works remain unclear. Nonetheless, the consistent results of clinical trials make a compelling case for the value of IP therapy in the treatment of women with advanced ovarian cancer.

We plan a broad-based dissemination and educational plan, in conjunction with the relevant professional societies, the NCI-designated Cancer Centers, the Clinical Trials Coopera-

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tive Groups that conducted these trials, and cancer advocacy groups. We welcome the help and expertise, for example, of the Society of Gynecologic Oncologists, the Gynecologic Cancer Foundation (GCF), the American Society of Clinical Oncology, the Society of Surgical Oncology, the American College of Obstetricians and Gynecologists, the Oncology Nursing Society, the Society of Gynecologic Nurse Oncologists, and the wide array of ovarian cancer advocacy groups brought together through the GCF's Allied Support Group and the Ovarian Cancer National Alliance. Focus groups of doctors and nurses active in the care of women with ovarian cancer have made clear the importance of specific guidance on how to place IP ports, administer chemotherapy via an IP route, and manage expected toxicities. Through the Gynecologic Cancer Intergroup we have worked to make these research findings and the NCI Clinical Announcement available outside the United States [8]. We have also begun to plan how best to evaluate use of IP therapy as part of the standard management of women with optimally debulked stage III ovarian cancer in practices across the US over the next few years.

The further development of IP therapy for women with ovarian cancer provides numerous research challenges. We need to investigate how to reduce the toxicity of IP administration while maintaining efficacy, to combine an IP approach with new chemotherapeutic and biologic agents, and to gain a better understanding of the biologic mechanisms by which IP therapy improves cancer control. In addition, we need to determine the benefit of IP administration in the consolidation setting, or after neoadjuvant chemotherapy followed by optimal cytoreductive surgery. While this research continues, however, we have a responsibility to ensure that women with advanced ovarian cancer who are candidates for IP therapy benefit from this treatment advance associated with such a remarkable improvement in overall survival.

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Edward L. Trimble*
Michaele C. Christian
Cancer Therapy Evaluation Program,
Division of Cancer Treatment and Diagnosis,
National Cancer Institute, Bethesda, MD 20892, USA
*Corresponding author.