

Practicing What We Preach!

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Epithelial ovarian cancer remains one of the most feared and lethal malignancies in women. It is the eighth most common cancer in women, but the fifth leading cause of cancer deaths.¹ In light of these statistics, it is important to implement all treatment approaches that have been shown to improve overall outcomes in this very lethal and morbid illness. Treatment with intraperitoneal chemotherapy has been shown to confer the best overall outcomes; however, surprisingly, it has not yet been widely adopted in this country as initial treatment despite published phase III data, an NCI alert, and national treatment guidelines with type 1 evidence advocating this approach.

In 1995, intraperitoneal chemotherapy was not mentioned in the first NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer. At that time, the accompanying guideline discussion published in *Oncology*² mentioned that the guideline panel thought that intraperitoneal chemotherapy should be considered investigational and offered only in clinical trials. However, shortly after this publication, large randomized phase III studies were published demonstrating the superior outcomes obtained when intraperitoneal chemotherapy was used in the upfront setting after surgical cytoreduction. The initial trial was published in December 1996,³ and compared treatment with intravenous cyclophosphamide and intravenous cisplatin versus intravenous cyclophosphamide and intraperitoneal cisplatin. Results showed that patients receiving the intraperitoneal chemotherapy had an 8-month improvement in median overall survival (OS). Importantly, a reduction in tinnitus, clinical hearing loss, and neuromuscular toxicity was seen in patients receiving cisplatin intraperitoneally compared with intravenously. It is important to understand that this trial was and remains the only trial to compare dose-equivalent cisplatin-containing regimens. However, it was not accepted as a practice-changing study despite showing improvement in OS with less toxicity, because by the time it was published paclitaxel had already been proven to be a superior second agent, and the oncology community felt that intraperitoneal chemotherapy was not necessary in the age of the taxanes. Annual discussions at the NCCN Ovarian Cancer Panel meetings between 1996 to 2000 were very contentious, and resulted in the addition of intraperitoneal chemotherapy as a category 3 recommendation (some panel members strongly felt this should not be recommended).

However, interested practitioners remained undaunted and a second phase III trial⁴ was designed comparing intraperitoneal and intravenous chemotherapy. This study, however, attempted to exploit the observation that patients with small-volume disease seemed to have improved outcomes when intraperitoneal chemotherapy was used, and was designed to chemotherapeutically cytoreduce patients by administering 2 cycles of moderately high-dose intravenous carboplatin (area under the curve, 9) before randomization to either intraperitoneal and intravenous chemotherapy. The results of this study were also striking, showing an 11-month improvement in OS in the intraperitoneal arm (63 vs 52 months). This was the first study to show that 5-year median survivals in advanced-stage ovarian cancer were achievable. However, the hematologic toxicity encountered in both arms because of the initial 2 cycles of intravenous high-dose carboplatin was significant, and the regimen as designed was not considered possible for routine use. Further guideline discussions were held, and by 2000 the recommendation for intraperitoneal chemotherapy in the upfront setting was upgraded to category 2B (general consensus that this was reasonable but not necessarily recommended by all).

The third randomized phase III study,⁵ published in 2006, however, showed an astonishing 17-month improvement in median survival in patients treated with intravenous followed by intraperitoneal chemotherapy compared with intravenous



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chemotherapy alone. This resulted in an NCI alert recommending that appropriate patients should be considered for intraperitoneal chemotherapy. The publication of these data resulted in a change in the NCCN Guidelines, designating intraperitoneal chemotherapy as a category 1 recommendation (randomized phase III evidence with high statistical power), where it remains today.⁶ However, the toxicity from the high-dose cisplatin used in the trial was substantial, and despite the large OS advantage, the high-level phase III evidence, and the subsequent publication of patient-reported outcomes data that suggested a poorer health-related quality of life during treatment but virtually equivalent quality of life, except for a mild difference in neurotoxicity, at 12 months after treatment,⁷ most patients with ovarian cancer are still not offered intraperitoneal chemotherapy.

Further evidence now shows improved outcomes in patients receiving intraperitoneal chemotherapy as upfront treatment for ovarian cancer. Data analyzed from the NCCN Oncology Outcomes Database and reported at the 2014 ASCO Annual Meeting⁸ examined treatment administered at NCCN Member Institutions, showing significantly improved outcomes in unselected patient populations. The 5-year OS rate was 62.5% in patients receiving intraperitoneal chemotherapy compared with 45.0% in those treated with intravenous chemotherapy, comparable with the rates reported in the study by Armstrong et al,⁵ showing that the improvement in outcome can be seen in an unselected patient population that is treated with standard chemotherapy off-study. Unfortunately, from 2007 to 2012, the percentage of patients receiving intraperitoneal chemotherapy declined, with fewer than 50% of eligible patients receiving intraperitoneal chemotherapy in 2012.

All oncologists desire to recommend and use the best treatment possible for their patients. This should not depend on the specialty of the initial chemotherapist, whether it is a gynecologic oncologist or a medical oncologist. In the latter case, continued close collaboration is important between the specialists to ensure that patients receive the best possible care. Selection of treatment should be largely determined by the clinical trial process, whereby one form of treatment is directly compared with other forms of treatment. End points of these processes include OS and/or progression-free survival, toxicity, and quality of life. OS has been and continues to be the gold standard for practice-changing research. It is unconscionable that nationally, most women with ovarian cancer are not offered intraperitoneal chemotherapy. It is incumbent upon NCCN Member Institutions to follow our own guidelines in this respect and change our practices based on the overwhelming evidence that this approach results in significantly improved outcomes for our patients.

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