Is There a Role for Intraperitoneal Chemotherapy in the Management of Ovarian Cancer?

By J. Tate Thigpen, MD [2]

Phase I and II clinical trial data have demonstrated the safety, pharmacokinetic advantage, and potential for enhanced cytotoxicity associated with the intraperitoneal administration of antineoplastic agents in the

Since the 1970s, dose intensity has been the siren song of the medical oncologist. Simply stated, the words of the song keep repeating: "More is better." The tendency of ovarian cancer is to spread via intraperitoneal dissemination and to remain grossly confined to the peritoneal cavity throughout much of its natural history. Fortunately or unfortunately, this tendency enables an alternative to stem cell-supported high-dose therapy, by which we can achieve even greater dose intensity.

Proof of Efficacy of Intraperitoneal Therapy

Gynecologic and medical oncologists have studied intraperitoneal chemotherapy for 22 years. Several observations over that time form the basis of intraperitoneal therapy. First, it is feasible to administer the most active agents for ovarian carcinoma directly into the peritoneal cavity. Second, in terms of peak drug levels, as well as area under the concentration-time curve (AUC), the intraperitoneal route offers significant pharmacokinetic advantages over intravenous (IV) administration. Third, significant systemic exposure to cisplatin (Platinol) is still achieved because the drug is taken up into the vascular compartment to a great extent. Fourth, phase I and II studies have reported numerous responses.

While these rationales were being drawn, however, several potential problems were largely downplayed: Extraperitoneal spread was not infrequent; drug was unevenly distributed in the peritoneal cavity because of adhesions; intraperitoneal drug had poor depth of penetration into larger (> 0.5 cm) nodules; and there was a lack of evidence of the value of doubling dose intensity instead of using the usual dose ranges of agents. These problems, along with the adverse effects that are unique to intraperitoneal therapy, as well as the more complex logistics of intraperitoneal drug administration, mandate that there be a clinically documented advantage to the intraperitoneal route in terms of efficacy before this approach is adopted as part of standard care.

As Dr. Markman correctly points out, the introduction of a more complex and potentially more toxic approach requires a positive randomized phase III trial. He cites three different clinical settings in which he believes intraperitoneal therapy would be a rational option for ovarian carcinoma (Table 4 of the Markman article). Many of the reports on which this is based, however, do not distinguish between patients who responded to front-line therapy (and hence can be expected to be chemosensitive) and those who failed to respond to front-line therapy.

Intraperitoneal Regimens as Second-Line Therapy

In a 1991 report, Dr. Markman and colleagues detailed studies of 72 patients treated with intraperitoneal platinum-based regimens after front-line therapy.[1] In those who responded to front-line therapy, a high response rate was observed (59%), whereas those who failed to respond to front-line platinum exhibited only a 9% response rate. Even in patients who were chemosensitive, IV platinum-based second-line therapy produced similar results. This raises serious questions about any defined role for intraperitoneal chemotherapy in the second-line setting. Most telling, there are no randomized phase III trials to establish any advantage for intraperitoneal therapy.

Intraperitoneal Therapy in the Front-Line Setting
In contrast to the second-line setting, three randomized phase III trials have compared IV and intraperitoneal regimens for front-line therapy.\cite{2-3; D. Armstrong, personal communication, 2000.} In his article, Dr. Markman discusses these extensively. The first of these, a Southwest Oncology Group (SWOG)/Gynecologic Oncology Group (GOG) trial\cite{2} compared IV cyclophosphamide (Cytoxan, Neosar) plus either IV or intraperitoneal cisplatin in patients with disease up to 2 cm in diameter. Results showed a statistically significant survival advantage for the intraperitoneal regimen. Unfortunately, however, this study suffers from several problems.

The initial goal of the study was to accrue 400 patients to seek a hazard ratio of 0.67. At the midpoint of accrual, the investigators decided to extend accrual to 650 patients to accrue sufficient patients with < 0.5-cm disease to allow a subset analysis on the basis that only these patients could be expected to benefit. The final analysis included all 650 patients and detected a significant hazard ratio of 0.77. The original goal of the study—a hazard ratio of 0.67—was never achieved. Furthermore, the subset of patients with < 0.5-cm residual disease did not significantly benefit from intraperitoneal therapy (median survival: 51 vs 46 months). These problems raise serious questions about any conclusion that the intraperitoneal regimen was superior.

The second study, a GOG-SWOG study\cite{3} compared IV paclitaxel (Taxol)/cisplatin to a dose-intensive regimen of two cycles of carboplatin (Paraplatin), AUC 9, followed by IV paclitaxel plus intraperitoneal cisplatin. This trial was never intended as a study of intraperitoneal vs IV therapy. Instead, the study compared a standard regimen to a dose-intensive regimen patterned after an approach developed at Memorial Sloan-Kettering Cancer Center. This study showed a significant improvement in progression-free survival; but the difference in survival is only of borderline significance. The dose-intensive regimen was significantly more toxic.

Thus, while it is true that two randomized phase III trials have shown a possible advantage for an intraperitoneal regimen, both studies have sufficient problems in that neither can serve as the basis for using intraperitoneal therapy as part of standard care. Dr. Markman perhaps stated it best: "Despite the observed toxicity, the results of this study continued to stimulate interest with regard to defining a role for intraperitoneal drug delivery in ovarian cancer." In short, even Dr. Markman feels there is no defined role for intraperitoneal therapy at this point.

The third trial, a GOG study\cite{4} compared IV paclitaxel/cisplatin to IV paclitaxel followed by intraperitoneal cisplatin and paclitaxel. This study\cite{which has completed accrual and is now maturing\}]\should answer once and for all whether intraperitoneal therapy plays any front-line role in ovarian cancer. In the absence of results from this third effort, however, intraperitoneal regimens should not be used for ovarian carcinoma outside of clinical trials.

If, after all of this, there remain skeptics who insist that intraperitoneal therapy has a proven advantage, such individuals should ask themselves these questions: If the issue were settled, why was a third trial necessary? If the advantages are clear, why do so few physicians dealing with ovarian carcinoma recommend intraperitoneal therapy? More is better, more is better, more is better. . . . It is, isn't it?

**References:**


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