

Intraperitoneal therapy for stage III optimally debulked ovarian cancer

Should women with optimally resected stage III ovarian cancer be treated with intraperitoneal (IP) cisplatin and a taxane rather than the universally accepted standard of care—a combination of intravenous (IV) carboplatin and paclitaxel? Three randomized clinical trials, the most recently published of which is described here, certainly point in that direction, with all three finding that IP chemotherapy is superior to IV administration in prolonging progression-free and overall survival. But IP chemotherapy is much more toxic than IV therapy and, according to the experts whose opinions follow, may not be a viable option for the kinds of patients seen by community oncologists.

A recently reported Gynecologic Oncology Group (GOG) trial^{1,2} showed a remarkable 15.9-month increase in median overall survival for intraperitoneal (IP) versus intravenous (IV) chemotherapy among patients with newly diagnosed stage III ovarian carcinoma or primary peritoneal carcinoma.

A total of 415 women with tumors that had been optimally debulked (no residual mass > 1 cm) were randomized to receive 135 mg/m² of paclitaxel IV over 24 hours followed by either (1) 75 mg/m² of cisplatin IV on day 2 or (2) 100 mg/m² of cisplatin IP on day 2 and 60 mg/m² of paclitaxel IP on day 8, with treatment being given every 21 days for 6 cycles. More than

80% of patients in both the IV and IP groups were between 41 and 70 years of age, most had a GOG performance status of 0 or 1, and 87% and 90%, respectively, had ovarian cancer. Rates of pathologic complete response among patients having second-look laparotomy were 41% in the IV group (35/85) and 57% in the IP group (46/81). Median durations of follow-up were 48.2 months in the IV group and 52.6 months in the IP group.

With regard to the trial's primary endpoints (Figure 1), progression-free survival was 18.3 months in the IV group versus 23.8 months in the IP group, representing a 20% reduction in risk of progression or death in the IP group (relative risk, 0.80; 95% confidence interval [CI], 0.64–1.00; *P* = 0.05), and median overall survival was 49.7 months versus 65.6 months, respectively, representing a 25% reduction in risk of death in the IP group (relative risk, 0.75; 95% CI, 0.58–0.97; *P* = 0.03).

The promising results with regard to progression-free and overall survival are somewhat tempered by the excess toxicity observed in the IP group (Table 1), with significantly more patients in this

TABLE 1

Grade 3 or 4 adverse events in the intravenous (IV) and intraperitoneal (IP) treatment arms

	Number (%) of patients		P value
	IV group (n = 210)	IP group (n = 201)*	
Leukopenia†	134 (64)	152 (76)	< 0.001
Platelet count < 25,000/μL	8 (4)	24 (12)	0.002
Other hematologic event	190 (90)	188 (94)	0.87
Gastrointestinal event	51 (24)	92 (46)	< 0.001
Renal or genitourinary event	5 (2)	14 (7)	0.03
Pulmonary event	5 (2)	7 (3)	0.50
Cardiovascular event	10 (5)	19 (9)	0.06
Neurologic event	18 (9)	39 (19)	0.001
Cutaneous change	2 (1)	2 (1)	0.96
Event involving lymphatic system	0 (0)	3 (1)	0.07
Fever	8 (4)	19 (9)	0.02
Infection	12 (6)	33 (16)	0.001
Fatigue	9 (4)	36 (18)	< 0.001
Pain	3 (1)	23 (11)	< 0.001
Hepatic event	1 (< 1)	6 (3)	0.05
Other	1 (< 1)	6 (3)	0.05

* In the IP group, four patients did not receive any protocol-based medication.

† White blood cell count < 1,000/μL

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Commun Oncol 2006;3:348–353

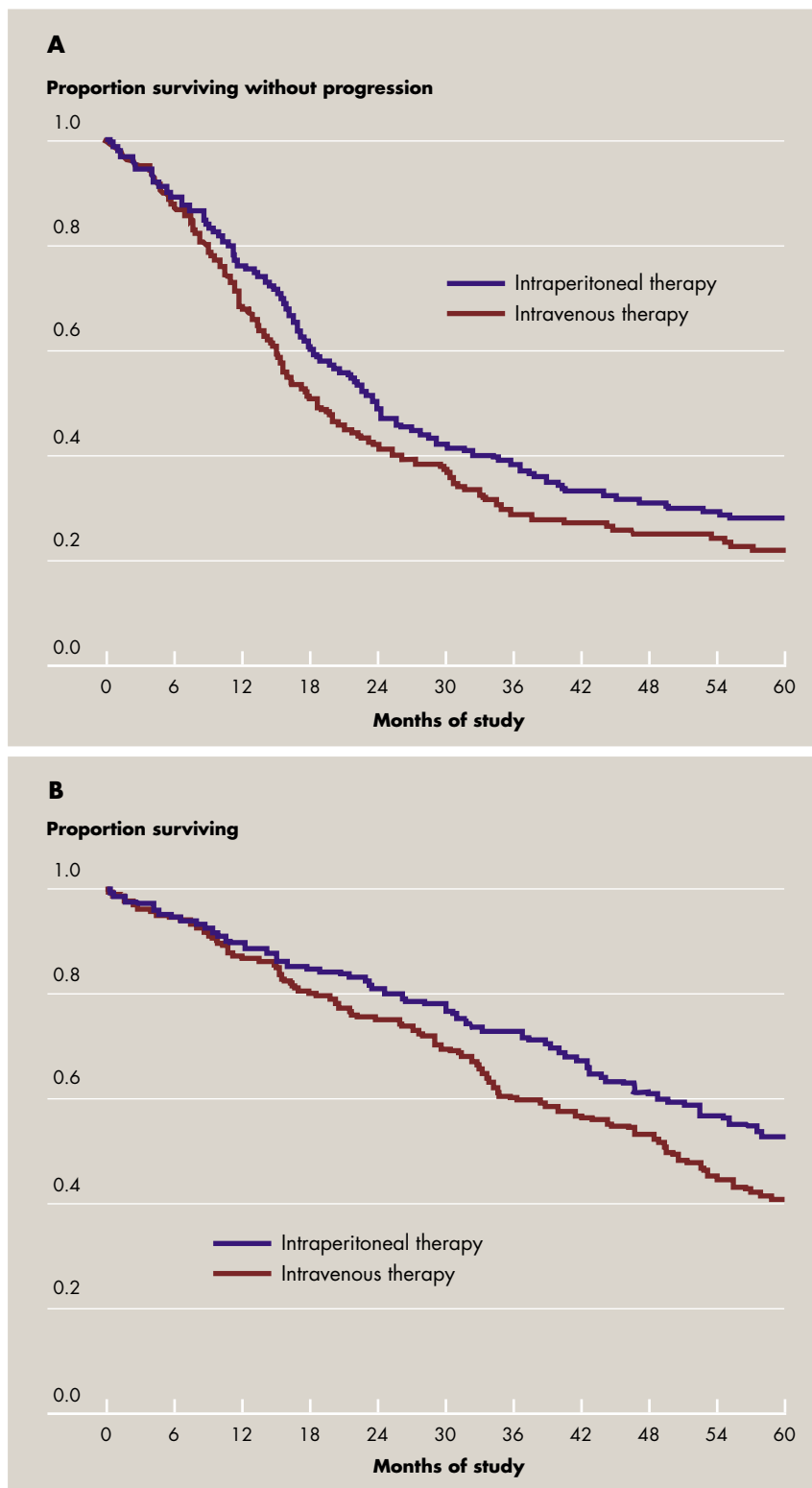


FIGURE 1 Progression-free survival (**A**) and overall survival (**B**) in the intraperitoneal and intravenous treatment arms of a Gynecologic Oncology Group study in patients with newly diagnosed, optimally debulked stage III epithelial ovarian cancer. Reproduced, with permission, from Armstrong et al.¹ Copyright © 2006 Massachusetts Medical Society. All rights reserved.

group having severe or life-threatening (grade 3 or 4) fatigue; pain; or hematologic, gastrointestinal, neurologic, or metabolic toxicities. Among the 210 patients in the IV group, 189 (90%) completed 6 cycles of chemotherapy, and 174 (83%) received all 6 cycles of IV therapy. In comparison, among the 205 IP patients, 170 (83%) completed 6 cycles, but only 86 (42%) completed 6 cycles of IP therapy and 48% received 3 cycles or less of IP therapy. The primary reason for discontinuing IP treatment was catheter-related complications. All nine treatment-related deaths, four in the IV group and five in the IP group, were attributed to infection, with three in the IP group also being attributed to the tumor.

Quality of life (QOL), as measured by the Functional-Assessment of Cancer Therapy–Ovarian (FACT–O) test instrument, was significantly worse at baseline in the IP group than in the IV group. Adjusted FACT–O scores showed that, compared with the IV group, the IP group had significantly worse QOL before treatment cycle 4 ($P < 0.001$) and 3–6 weeks after treatment ($P = 0.009$) but not 1 year after treatment.

These findings raise important questions. Can the benefits of IP treatment be preserved without the excess toxicity? The finding of such a large survival benefit despite the fact that nearly half of the patients received only 3 of the 6 planned IP cycles suggests that benefit is achieved early in treatment. Can this finding be translated into a strategy for providing shorter duration and less toxic IP therapy?

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Intravenous chemotherapy with carboplatin/paclitaxel is the standard of care for patients with optimally resected stage III ovarian cancer

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IN JANUARY 2006, the National Cancer Institute (NCI) issued a clinical announcement stating that women with optimally debulked stage III ovarian cancer “should be counseled about the clinical benefit associated with combined IP and IV administration of chemotherapy” and that “strong consideration should be given to a regimen containing IP cisplatin (100 mg/m²) and a taxane.”¹ This clinical alert was timed with a publication by Armstrong et al² that described the results of Gynecologic Oncology Group (GOG) protocol 172, which compared intraperitoneal (IP) therapy with intravenous (IV) cisplatin/paclitaxel. As described in the clinical announcement, this trial was the third randomized trial to demonstrate an improvement in overall or progression-free survival for patients treated with an IP regimen compared with IV chemotherapy.^{3,4}

On the face of it, three randomized trials, all reporting similar outcomes, should have established a new standard of care. However, controversy still exists and is based primarily on the toxicity of IP chemotherapy and the fact that IP chemotherapy has never been prospectively compared against what is universally accepted to be the standard of care for patients with ovarian cancer—a combination of IV carboplatin and paclitaxel.⁵

The NCI clinical announcement

did not mandate a change in practice but, instead, recommended that patients should be “counseled” and physicians should give “consideration” to IP therapy. Furthermore, the NCI announcement recommends that IP therapy “should be abandoned and the patient treated with IV chemotherapy” in the face of “unacceptable pain or extremely slow infusion” and “severe complications” such as “intra-abdominal infection, prolonged ileus, bowel obstruction, or bowel perforation.”¹ It even recommends that a malfunctioning IP catheter should not be replaced when it is associated with any other significant toxicity, the patient being switched to IV chemotherapy instead. These recommendations are based on the extreme toxicities associated with IP chemotherapy, which permit only a minority of patients to complete all 6 cycles of scheduled treatment.⁶

Moreover, the NCI alert did not recommend a specific regimen for administration nor an optimal number of IP treatments. Some experts have recommended that it is acceptable to decrease the dose of cisplatin to 75 mg/m² (despite the NCI announcement that consideration should be given to a 100 mg/m² IP dose)¹ and that the day 8 IP paclitaxel dose could also be possibly eliminated.⁷ Although it is self-evident that decreasing the dose of toxic cytotoxic agents and eliminating an extra day of drug administration will decrease the toxicity of treatment, if there is a benefit

to IP therapy, then surely such major modifications in the regimen should be prospectively tested before it can be established that they do not decrease efficacy of treatment.

Is IP chemotherapy better than standard IV carboplatin/paclitaxel?

Even more important than toxicity considerations is the fact that IP chemotherapy has not been prospectively compared with IV carboplatin/paclitaxel in any randomized trial. Neither the NCI’s clinical announcement nor the study reported by Armstrong et al² compared the results of IP therapy with what can be achieved with IV carboplatin/paclitaxel in the same group of patients. GOG 158 reported a 16% reduction in the hazard ratio for death, as well as significantly less toxicity, for patients treated with carboplatin/paclitaxel versus those given cisplatin/paclitaxel.⁸ Together with the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) trial,⁹ GOG 158 clearly established that the standard of care for patients with ovarian cancer was IV carboplatin/paclitaxel. All major clinical trial groups throughout the world developing new treatments for ovarian cancer are utilizing carboplatin/paclitaxel as the control arm and not cisplatin/paclitaxel, as was used in GOG 172. In GOG 158, there was an improvement in median survival of 8.7 months (risk ratio, 0.84; 95%

confidence interval, 0.70–1.02) for patients treated with carboplatin/paclitaxel versus those treated with cisplatin/paclitaxel. Unfortunately, since the results of GOG 158 were not known when GOG 172 was developed, the control arm was cisplatin/paclitaxel and not carboplatin/paclitaxel.

Cross-trial comparisons are not definitive but are nevertheless informative and hypothesis generating. In particular, GOG 158 and GOG 172 were sequential protocols that used identical eligibility criteria and were performed by the GOG over a relatively short period. In such a cross-trial comparison, there are minimal differences in overall outcome. Instead of an improvement in overall median survival of 15 months, the difference may only be 8.2 months. In addition, median survivals can overestimate the differences due to the relatively small number of events at this point. A comparison of the actuarial survival curves from patients treated with IV carboplatin/paclitaxel compared with IP therapy in GOG 172 reveals no difference in 2-year survival and only a 4%–5% difference in 4-year survival. Furthermore, it does not appear that there would be significant difference in the relative risk since the shape of the actuarial curves is very similar. It needs to be reemphasized that this cross-trial comparison, though not definitive, is robust due to the large number of patients treated on sequential protocols using identical eligibility criteria. Both trials used IV cisplatin/paclitaxel as the control arm without any significant difference in outcome.

Should community oncologists recommend IP chemotherapy?

What does all this mean for the practicing oncologist? There does not appear to be a mandate that all patients with optimal stage III ovarian cancer receive IP chemotherapy. The

GOG is performing phase I/II trials of different IP regimens to determine whether their toxicity can be decreased. However, these phase II trials will not establish the true efficacy of any new, less-toxic IP therapy. The community oncologist treating a woman with optimally resected stage III ovarian cancer cannot presently offer her a regimen that has been shown to have acceptable toxicity and which is recommended by the NCI. As previously described, the NCI clinical alert recommends IP cisplatin (100 mg/m²) and a taxane, whereas some authorities suggest that this regimen can be markedly modified to decrease its toxicity but without providing any evidence of how that will influence outcome.⁷

Another important consideration for the community oncologist is the fact that, in practice, more elderly patients often present with comorbid illnesses and are not eligible for randomized clinical trials. It is possible that the toxicities of chemotherapy may be even greater in these patients, and selection criteria remain controversial for IP therapy. The bottom line is that no survival advantage has been reported for IP therapy compared with standard IV carboplatin/paclitaxel in patients with optimally debulked stage III disease. Unfortunately, IP therapy with its formidable toxicity led to a clinical announcement by the NCI before it was prospectively compared with a much less toxic, more convenient regimen of IV carboplatin/paclitaxel, which, in a robust exploratory cross-trial comparison, appears to have very similar efficacy. Until a clearly defined IP regimen with acceptable toxicity is shown to be superior to IV carboplatin/paclitaxel in a prospective randomized trial, the latter combination remains an acceptable standard of care for the community oncologist treating patients with optimal stage III ovarian cancer.

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Intraperitoneal chemotherapy as primary treatment of advanced ovarian cancer

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OVER THE PAST 2 DECADES investigators at a number of centers have explored the potential of intraperitoneal (IP) antineoplastic drug delivery as a management strategy for patients with ovarian cancer.¹ More recently, publication of the results of three well-designed and conducted randomized phase III clinical trials, all demonstrating a survival benefit associated with the regional administration of cisplatin-based chemotherapy, has led the National Cancer Institute (NCI) to conclude that, following an attempt at maximal surgical cytoreduction, women with *small-volume, residual, advanced ovarian cancer* should be offered this approach as a primary management strategy.²⁻⁴

What are the data to support this conclusion, and how can the results of these clinical trials be translated into routine clinical practice?

The three multicenter trials were conducted by NCI-sponsored cooperative groups (Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group). Each study employed a “standard” intravenous (IV) cisplatin-based control arm (routinely utilized when each study was conducted) and an experimental regimen that included IP cisplatin.²⁻⁴

Although the details of these studies differed (eg, use of a “second” IV or IP drug in the treatment regimen), the results of the trials did not, with each study demonstrating an improvement in overall survival associated with the regional ap-

proach. The *relative reduction in the risk of death* associated with IP cisplatin delivery was remarkably consistent between the studies, ranging from 20% to 30%. The most recently reported phase III trial revealed a 16-month improvement in median overall survival associated with regional cisplatin-based therapy versus IV cisplatin-based therapy.⁴

Concerns with IP chemotherapy

Although the evidence-based data supporting the administration of IP chemotherapy are substantial, several clinically relevant issues related to the routine use of this management strategy have been raised. These concerns fall into three general categories: (1) “excessive” toxicity, (2) catheter problems, and (3) lack of experience with the regional drug-delivery technique.⁵

Systemic toxicity of cisplatin

The majority of the toxicity concerns result from the use of cisplatin, rather than carboplatin, in the regional treatment program, and the added systemic side effects associated with the administration of the older, first-generation platinum compound. However, it is critical to note here that *oncologists do know how to deliver cisplatin*, and before the availability of carboplatin, cisplatin was one of the most frequently employed antineoplastic agents in routine oncologic practice.

Further, with the use of increasingly more effective antiemetic agents and regimens, appropriate delivery of required hydration programs, and rec-

ognition of the potential for neurotoxicity associated with the combination of cisplatin and paclitaxel, it is well established that cisplatin-based IP strategies can be administered with acceptable toxicity profiles. In fact, although a greater short-term negative impact on quality of life was demonstrated in the IP arm of the most recently reported phase III randomized trial,⁴ 1 year after the completion of therapy there was no difference between IP and IV cisplatin/paclitaxel in this highly clinically relevant parameter.

Catheter-related side effects

The truly different aspect of this management strategy is the requirement to access the peritoneal cavity—and the potential for associated morbidity. Although it would be inappropriate to conclude that an “optimal catheter” delivery system has been devised or that definitive guidelines for catheter placement and maintenance have been developed, existing data unquestionably demonstrate this approach can be safely, and routinely, employed in the non-tertiary care setting (as revealed by the results of the multicenter cooperative group phase III clinical trials).²⁻⁵

Experience with IP chemotherapy

Finally, it must be acknowledged that there is a legitimate “learning curve” for this strategy, and it may not be appropriate for all oncology practices to develop the expertise to treat the “type of patient needing IP therapy” if a particular physician

or group sees such a patient once a year, or even less frequently.

Just as an oncology group would refer an appropriate lymphoma patient to a larger center for a bone marrow transplant, it may be decided that a woman with small-volume residual advanced ovarian cancer should be referred to a practice that sees a larger number of patients in this disease category, which will permit that practice to justify the training—and maintenance of expertise—necessary to employ this treatment strategy. It is important to note that this determination, whether to treat a woman with IP therapy or refer

the patient, should be a decision of individual oncology groups as they consider what is truly in the best interest of their patients.

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