COMMENTARY

Results of the 2006 Innsbruck International Consensus Conference on Intraperitoneal Chemotherapy in Patients With Ovarian Cancer

Christian Marth, MD[1]
Joan L. Walker, MD[2]
Richard R. Barakat, MD[3]
Antonio Casado, MD[4]
Angiolo Gadducci, MD[5]
Brigitte Miller, MD[6]
Franco Odicino, MD[7]
Eric Pujade-Lauraine, MD[8]
Jalid Sehouli, MD[9]
Claes Tropé, MD[10]
Lari Wenzel, MD[11]
Alain G. Zeimet, MD[1]

[1] Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria.

[2] Department of Obstetrics and Gynecology, Oklahoma University of Health Science, Oklahoma City, Oklahoma.

[3] Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center, New York, New York.

[4] Department of Medical Oncology, University Hospital, San Carlos, Madrid, Spain.

[5] Department of Obstetrics and Gynecology, University of Pisa, Pisa, Italy.

[6] Department of Obstetrics and Gynecology/Section of Gynecologic Oncology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

[7] Division of Gynecology and Obstetrics, University Brescia, Brescia, Italy.

[8] Hopital Hotel Dieu, Paris, France.

[9] Department of Gynecology and Obstetrics, University Charity Hospital, Berlin, Germany.

[10] Gynecologic Department, The Norwegian Radium Hospital, Oslo, Norway.

[11] Health Policy Research, College of Medicine, University of California-Irvine, Irvine, California.

See related article on pages 692–702, this issue.

The 2006 Innsbruck International Consensus Conference was supported by unrestricted grants from AESCA GmbH, AMGEN Gmbh, ARROW International, Bristol-Myers Squibb GmbH, EBEWE Pharma GmbH, GlaxoSmithKline Pharma GmbH, Johnson & Johnson/Ethicon, NOVARTIS Pharma GmbH, ROCHE Austria GmbH, Sanofi Aventis GmbH, and SMITHS Medical Osterreich GmbH.

We thank the scientific secretary, Ms. Ingrid Zeimet-Kirchmair, Dr. Daniel Egle, Dr. Michael Hubalek, Dr. Nicole Concin, Dr. Julia Seeber, and Mr. Thomas Jenewein for technical and organizational help.

Address for reprints: Christian Marth, MD, Department of Obstetrics and Gynecology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria; Fax: (011) 43-512-50423055; E-mail: christian.marth@uibk.ac.at

Received October 17, 2006; revision received November 13, 2006; accepted November 13, 2006.

International evidence-based consensus statements are important for defining standards of care and developing guidelines for communities worldwide. For ovarian cancer, successful international consensus meetings have been organized, and the most important was the meeting in Baden-Baden, Germany, in September 2004, which was organized by the Gynecological Cancer Intergroup. Its statements still are valid and are applied in daily routine.[1]

DOI 10.1002/cncr.22467
Published online 19 January 2007 in Wiley InterScience (www.interscience.wiley.com).

This consensus also included the role of intraperitoneal (IP) therapy. Although randomized Phase III clinical trials are addressing the IP route for cisplatin therapy in patients with minimal disease, interpretations of those results remain controversial. Thus, IP cisplatin has not been adopted widely[2–4] (level of acceptance, 13 of 13 panelists).

However, published results from the Gynecologic Oncology Group (GOG) Trial 172 indicated that patients who received part of their chemotherapy through the IP route had a median survival that was 16 months longer than that of women who received intravenous (IV) chemotherapy alone (65.6 months vs 49.7 months).[5] In addition, a meta-analysis by the Cochrane collaboration was published and included 9 clinical trials. Ultimately, 8 of those trials met the criteria for analysis and confirmed the benefit of IP chemotherapy over standard IV regimens. The authors of that report described a hazard ratio of 0.79 for the time to progression and the time to death, reflecting a significant survival advantage, although major side effects and complications have been reported.[6] Based on these findings, the National Cancer Institute issued an announcement encouraging the treatment of advanced ovarian cancer with anticancer drugs after surgery, including IP therapy.[7] The combined method, which delivers drugs into a vein and directly into the abdomen, extends overall survival for women with advanced ovarian cancer by approximately 1 year. This announcement also was supported by other important societies. Beth Karlan, Society of Gynecologic Oncologists (SGO) president and director of the Women's Cancer Research Institute of the Division of Gynecologic Oncology at the Cedars-Sinai Medical Center, stated that IP chemotherapy should be considered by oncologists for women who have undergone optimal surgical resection for ovarian cancer (see http://www.ccopnet.com/ccop/docs/IntraperitonealPressRelease_010406.pdf). In view of these very important findings and recommendations, the statement on first-line therapy that was made by the last ovarian cancer consensus conference should be reevaluated. For this purpose, international experts in ovarian cancer treatment met in Innsbruck to develop a structured consensus procedure that would allow the development of recommendations with high acceptance. Participants were selected for their international expertise, membership in steering committees of important gynecologic oncologic societies, and recent publications on ovarian cancer treatment. The most relevant questions were prepared according to suggestions from all authors.

Questions that had been prepared by discussion participants or panelists were presented, discussed, and voted on. They were converted to statements and were confirmed by the panelists after reading.

IP chemotherapy should be offered as an option for optimally debulked ovarian cancer patients (level of acceptance, 8 of 12 panelists): IP chemotherapy in patients with ovarian cancer who have undergone optimal debulking has an impact on both progression-free survival and overall survival compared with IV cisplatin and paclitaxel. Because of specific the problems and complications involved with IP chemotherapy, it cannot be considered the new standard, although it should be proposed to patients as a valid alternative. It is obvious that IP therapy can be administered only in specialized centers that have experience with the management of typical side effects and complications.

IP therapy should be proposed for patients with International Federation for Gynecology and Obstetrics (FIGO) stage III disease who have undergone debulking and have residual disease (greatest dimension, <1 cm). Patients who have FIGO stage IV disease with pleural effusions only and minimal residual disease also may be good candidates for IP therapy. The presence of retroperitoneal lymph node metastasis is not a contraindication for IP therapy (level of acceptance, 10 of 12 panelists).

Hysterectomy is a clear standard in debulking surgery for ovarian cancer patients. However, removal of the uterus and opening of the vagina may promote loss of IP-instilled fluid. Thus, a subtotal hysterectomy may be an alternative. Meticulous closure of the vaginal cuff by continuous suture is sufficient in the majority of patients. The panelists therefore recommend a total hysterectomy as surgery of choice for patients in whom IP therapy is planned (level of acceptance, 12 of 12 panelists).

Preclinical and clinical data strongly indicated that, as noted previously, the optimal patient to profit from the extremely high concentrations of cytotoxic drugs in the peritoneal cavity would be the patient with a small amount of bulky disease present when this approach was initiated. Although it may be argued that several cycles of intense, systemic chemotherapy should be delivered to reduce residual tumor volume before starting IP treatment, this *chemical debulking* may improve the efficacy of locoregional therapy. Markman et al reported on a trial in which the experimental arm consisted of 2 courses of single-agent, high-dose, IV carboplatin (area under the curve, 9) before IP cisplatin (100 mg/m^2) and IV paclitaxel (135 mg/m^2 for 24 hours) were initiated.[8]

These findings were discussed by the panel, and there was general consensus that *chemical debulking* is sometimes favorable as initial chemotherapy before IP therapy. However, inefficient cytoreduction by high-dose chemotherapy often was associated

with bone marrow suppression, which makes sufficient IP administration of chemotherapy impossible and markedly reduces a patient's quality of life and performance status. The panel concluded that there is no reason to initiate moderate-dose, intense, systemic chemotherapy to debulk the tumor before IP therapy (level of acceptance, 11 of 12 panelists).

In the same context, it is very important to discuss whether patients who receive successful neoadjuvant, standard IV therapy are eligible for IP therapy after successful surgery and optimal debulking. The majority of panelists agreed that this is an interesting approach, although no data are yet available to answer this question. Therefore, there was general agreement not to exclude these patients from IP therapy (level of acceptance, 12 of 12 panelists). However, 45% of panelists recommended further studies in this subgroup, whereas the remaining panelists suggested that extrapolation of available data is also sufficient to introduce IP therapy into neoadjuvant treatment strategies.

Consolidation treatment after achieving complete remission induced by standard IV chemotherapy is an important issue. Recent data suggest that paclitaxel IV given for 1 additional year prolonged progression-free survival. Conversely, no conclusive studies have been published for IP therapy. The European Organization for Research and Treatment of Cancer initiated a study in which 4 cycles of cisplatin were administered IP in patients with ovarian cancer to achieve complete remission after platinum-based therapy.[9] However, that study was closed early because of slow recruitment, and the published results clearly were underpowered. In detail, 8-year progression-free survival and overall survival were similar in patients who received IP cisplatin and in patients who received no further treatment (38% vs 37% and 53% vs 48%, respectively). Indeed, when addressing the important quality-of-life results from GOG Trial 172, it is apparent that IP therapy may be associated with significant quality-of-life disruption during the active treatment phase; however, this would depend on drug, dosage, and delivery mechanisms.[10] Therefore, the majority of panelists advised that IP therapy currently should not be used for consolidation after the completion of standard IV therapy (level of acceptance, 8 of 12 panelists).

The panel also discussed whether elderly patients should be eligible for IP treatment. There was general consensus that the main issue, of course, is not age but performance status. Patients who are determined to be fit for IV therapy also can be treated with IP therapy.

With level of acceptance of 8/12, the panelists agreed to treat elderly patients. Two patients would no longer envisage this treatment in patients aged >70 years, and 2 panelists would treat patients up to age 80 years.

Another question addressed whether patients with carcinoma of the fallopian tube also should receive treatment with IP therapy. The panelists agreed that separate studies are not needed for this disease because of the low number of available patients and the fact that a clinical distinction between ovarian cancer and fallopian tube cancer is very difficult. Patients with cancer of the fallopian tube should be treated with IP therapy using the same rules that are used to treat patients with ovarian cancer (level of acceptance, 12 of 12 panelists).

In GOG Trial 172, only 42% of patients completed all 6 cycles. Nevertheless, a significant difference in survival was achieved. Although no data are available, the majority of panelists agreed that there should be a relation between the number of cycles and treatment success. Therefore, 6 cycles of IP therapy should be the objective (level of acceptance, 11 of 12 panelists). One panelist suggested that 2 to 4 cycles also would be sufficient for achieving optimal results. It was suggested that 1 cycle of IP therapy would not have a significant effect. This recommendation, however, must await trials comparing different numbers of IP treatments.

Clinical trials did not address the role of IP therapy sufficiently in patients with recurrent disease.[11] However, the panelists agreed that secondary cytoreduction after long progression-free survival may induce a situation in which IP therapy could be considered (level of acceptance, 9 of 12 panelists).

Only 3 panelists would consider IP therapy irrespective of its role in the treatment of recurrent disease. Diffuse peritoneal carcinomatosis or bulky recurrent disease, however, should not be an indication for IP therapy.

A remarkable number of problems associated with IP therapy are caused by delivery.[12] In particular, port systems have been known to involve catheter obstruction, skin infection, or bowel perforation. The majority of published trials have used implantable catheter systems. Panelists recommend the use of venous access with a large silicon tube (level of acceptance, 8 of 12 panelists). However, use of either the venous catheter or the peritoneal catheter is acceptable until future studies indicate a preference of 1 over the other. Direct injection, for example, using a Verres needle, was suggested by 2 of 12 panelists, and application of peritoneal catheter systems was also recommended by 2 of 12 panelists. The catheter should be placed at primary surgery (level of acceptance, 10 of 12 panelists).

TABLE 1
Role of Cytotoxic Agents in Intraperitoneal Therapeutic Regimens

Drug	Level of acceptance*			
	Recommended for use	Additional trials necessary before	Not expected to play a role	Might play a role, but only given IV in combination with other drugs given IP
Cisplatin	11/12	1/12	—	—
Carboplatin	—	12/12	—	—
Other platinum compounds	—	12/12	—	—
Paclitaxel	5/12	7/12	—	—
Albumin-bound paclitaxel (ABI 007)	—	12/12	—	—
Docetaxel	—	12/12	—	—
Topotecan	—	12/12	—	—
Gemcitabine	—	12/12	—	—
Interferons/cytokines	—	11/12	1/12	—
Chemohyperthermia	—	7/12	5/12	—
Radioactive conjugates	—	2/12	10/12	—

IV indicates intravenous; IP, intraperitoneal.
*Numbers indicate how many of 12 panelists agreed on each item.

However, because a short delay in chemotherapy will not lessen outcome, placement of the catheter during the first 4 postoperative weeks was considered sufficient, as suggested by 2 of 12 panelists. However, with regard to possible contamination by microorganisms, implantation of a foreign body is regarded dangerous. Because bowel surgery frequently is performed in patients with ovarian cancer to achieve optimal debulking, careful evaluation of these patients is necessary. However, panelists could not agree on this issue.

Six panelists were against placement of a catheter at the same time as colon surgery. Conversely, the panelists did not consider small intestine surgery a contraindication.

One important question is the time of treatment initiation. There is no role for intraoperative IP therapy, eg, cisplatin instillation (level of acceptance, 11 of 12 panelists).

Conversely, the panelists agreed to start IP therapy after patients recover from postoperative ileus (level of acceptance, 7 of 12 panelists) or after approximately 2 weeks (proposed by 4 of 12 panelists). Because there is no strict correlation between the initiation of chemotherapy and outcome, there is no reason to start IP therapy very early considering its known side effects.

There was great consensus of opinion that cisplatin is the substance of choice for IP therapy. It is important to mention that, although side effects (Table 1) would be more manageable with carboplatin, it cannot substitute for cisplatin. In the case of paclitaxel, the majority of panelists recommended continuing with further trials, although there is a very good rationale for using paclitaxel, because there is a major difference in the peritoneal plasma ratio. For the majority of other substances there is not enough experience to recommend application outside clinical trials.[13,14] Although there is some experimental evidence that hyperthermia may augment the efficacy of IP-administered substances, the majority of panelists do not see a role for this type of treatment in future. The reasons are mainly the complicated mode of administration and the increased toxicity.

Because IP therapy also impairs bone marrow function, administration of colony-stimulating factors or erythropoietins may be necessary. In the special case of IP therapy, the consensus was to apply these substances using the same rules that are used for IV therapy (level of acceptance, 10 of 12 panelists).

Adhesions are a major problem in IP therapy, because they can impede equal distribution of the cytotoxic agents throughout the whole peritoneal cavity. Nevertheless, 6 of 12 panelists do not recommend any diagnostic procedures concerning even distribution in IP-treated patients if the drug is easily deliverable. Only a minority recommends ultrasound or radioisotopes to monitor the distribution of IP medication.

Renal toxicity is among the most important side effects of cisplatin. Therefore, it is very important to use a prehydration protocol to prevent this toxicity. The same protocol that is used for IV cisplatin also is applicable for IP cisplatin (level of acceptance, 12 of 12 panelists), and it is not necessary to alter or adapt the application of fluids, because they may be resorbed in a

delayed fashion and because IP and IV cisplatin have different pharmacokinetics. The glomerular filtration rate (GFR), of course, is a crucial parameter in allowing cisplatin application. In the application of IP cisplatin therapy, a GFR $\geq$50 mL per minute is required (level of acceptance, 8 of 12 panelists). The minority of panelists also allow IP cisplatin therapy in patients who have lower GFR values.

Regarding quality of life, the neurotoxicities associated with IP therapy are of great importance.[10] Eleven of 12 panelists agreed that this toxicity is of very great or great importance and should be evaluated carefully. It is recommended that patients be informed about this increased toxicity to permit decision making.

Of course, the administration of IP therapy is more complicated than the administration of IV therapy. More experience in and knowledge of gynecologic oncology are necessary for this specialized treatment. Twelve of 12 panelists agreed that $\geq$10 IP applications are required per year to ensure a minimal standard of care for patients. Eight of 12 panelists requested >20 treatments per year.

The tumor marker CA-125 is produced and released by ovarian cancer cells.[15] However, peritoneal cells also contain a large amount of this protein. It is well known that processes in the peritoneum such, as inflammation, markedly increase CA-125 release.[16] Therefore, it may be argued that CA-125 tumor marker determination is not reliable in patients who receive IP treatment. However, 7 of 12 panelists agreed that, even if a blood sample is not taken immediately after IP instillation, CA-125 still is a reliable tumor marker. However, the CA-125 serum level should be evaluated carefully to exclude any influence by treatment route.

In view of these overwhelming data that demonstrate a survival benefit for patients who receive IP chemotherapy, the question is raised whether, eg, a GOG Trial 172 IP arm should be used as a control arm in all future clinical trials. For practical reasons, only 6 of 12 panelists voted for an obligatory IP control arm. It is obvious that, in the future, IV therapy will continue to play a role.

The International Consensus Conference on Intraperitoneal Chemotherapy in Ovarian Cancer Patients, which was held in Innsbruck, Austria, from February 17 to February 28, 2006, provided the first worldwide consensus after publication of the National Cancer Institute alert. A consensus on important questions regarding the standard of care in IP therapy was obtained. It is hoped that the high level of acceptance will help implement the consensus statement worldwide and that this is useful information on the role of IP therapy. Further evaluation of the results of this consensus meeting is necessary.

REFERENCES

1. du Bois A, Quinn M, Thigpen T, et al. 2004 Consensus statements on the management of ovarian cancer: final document of the third International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference, GCIG OCCC 2004. *Ann Oncol*. 2005;16(suppl 8):viii7–viii12.
2. Alberts DS, Liu PY, Hannigan EV, O'Toole R, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335:1950–1955.
3. Gadducci A, Carnino F, Chiara S, et al. Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. *Gynecol Oncol*. 2000;76:157–162.
4. Markman M. Role of intraperitoneal chemotherapy in the front-line setting. *J Clin Oncol*. 2003;21:145s–148s.
5. Armstrong D, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006; 354:34–43.
6. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2006;1:1–28.
7. National Cancer Institute. Clinical announcement – intraperitoneal chemotherapy for ovarian cancer. Available at URL: http://ctep.cancer.gov/highlights/clin_annc_010506.pdf.
8. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergoup study of the Gynecologic Oncology Group, Southwestern Oncology Group and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001;19:1001–1007.
9. Piccart MJ, Floquet A, Scarfone G, et al. Intraperitoneal cisplatin versus no further treatment: 8-year results of EORTC 55875, a randomized Phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based intravenous chemotherapy. *Int J Gynecol Cancer*. 2003;13(suppl 2):196–203.
10. Wenzel L, Huang H, Armstrong D, et al. Quality of life (QOL) results of randomized trial of intravenous (IV) paclitaxel and cisplatin vs. IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group Study. [abstract]. *Proc Am Soc Clin Oncol*. 2004;23:454. Abstract 5026.
11. Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. *J Clin Oncol*. 2006;24:988–994.
12. Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a Phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2006;100:27–32.
13. Pujade-Lauraine E, Guastalla JP, Colombo N, et al. Intraperitoneal recombinant interferon gamma in ovarian cancer patients with residual disease at second-look laparotomy. *J Clin Oncol*. 1996;14:343–350.
14. Zeimet AG, Marth C. Why did *p53* gene therapy fail in ovarian cancer? *Lancet Oncol*. 2003;4:415–422.
15. Rustin GJS, Timmers P, Nelstrop A, et al. Comparison of CA-125 and standard definitions of progression of ovarian cancer in the intergroup trial of cisplatin and paclitaxel versus cisplatin and cyclophosphamide. *J Clin Oncol*. 2006;24:45–51.
16. Zeimet AG, Offner FA, Marth C, et al. Modulation of CA-125 release by inflammatory cytokines in human peritoneal mesothelial and ovarian cancer cells. *Anticancer Res*. 1997;17:3129–3132.