Intraperitoneal Chemotherapy in Patients with Advanced Ovarian Cancer: The Con View

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Key Words. Ovarian neoplasms • Chemotherapy • Intraperitoneal

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Assess the rationale behind using i.p. chemotherapy for epithelial ovarian cancer patients and critically evaluate the data supporting its use.
2. Interpret the argument that i.p. chemotherapy cannot be accepted as standard of care for first-line systemic treatment of advanced ovarian carcinoma.
3. Determine which epithelial ovarian cancer patients may be appropriate for i.p. chemotherapy.
4. Avoid and/or manage the toxicities observed with i.p. chemotherapy.

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The CME activity for this article consists of material from both “Intraperitoneal Chemotherapy in Patients with Advanced Ovarian Cancer: The Con View” (Vergote et al.) and “Intraperitoneal Chemotherapy for Women with Epithelial Ovarian Cancer” (Trimble et al.).

ABSTRACT

Objectives. In this paper we wish to present the reasons why i.p. chemotherapy cannot be accepted as standard of care for first-line systemic treatment of advanced ovarian carcinoma.

Methods. The recent literature on i.p. chemotherapy is critically reviewed. All possible arguments against i.p. chemotherapy are reviewed.

Conclusions. Intraperitoneal chemotherapy is associated with a higher toxicity rate than i.v. chemotherapy. For this reason, none of the regimens investigated in the three Gynecologic Oncology Group (GOG) studies can be used as standard treatment outside clinical protocols. The trials on i.p. chemotherapy have suggested a survival difference. However, in the two most recent trials, i.p. chemotherapy or not was not the only research question because different schedules and dosages were used. In addition, the significance of the most recent GOG 172 study was only weak (p = .03), and the result was non-significant for progression-free survival. Intraperitoneal chemotherapy should be used only in the context of properly designed clinical trials. These trials must either assess i.p. therapy in comparison with the stan-
Standard treatment or address the issue of route of administration for equivalent dosages and schedules of the same drugs, and not a mosaic of these questions. In addition, these trials should investigate i.p. regimens that are less toxic than the regimens used in the three GOG trials, and which can be combined with molecular targeted therapies. The Oncologist 2008;13:410–414

INTRODUCTION
In September 2005, a Gynecologic Cancer Intergroup (GCIG) consensus meeting was held with the 13 national or international cooperative groups in Baden-Baden, Germany. One of these groups was the Gynecologic Oncology Group (GOG). During this consensus meeting, it was unanimously decided that, in addition to optimal debulking surgery, the standard systemic treatment for advanced ovarian carcinoma was carboplatin dosed to an area under the concentration–time curve (AUC) of 5–7.5, in combination with paclitaxel at a dose of 175 mg/m² given over 3 hours, every 3 weeks for six cycles [1].

A National Cancer Institute (NCI; Bethesda, MD) statement posted on the internet [2] proclaimed a change in practice on January 4, 2006, and concluded that, following optimal debulking, patients with ovarian cancer of Fédération Internationale de Gynécologie et d’Obstétrique stage III should be informed about the advantages associated with i.p. chemotherapy. The NCI announcement was based on the latest GOG study that was published on the same day in the New England Journal of Medicine [3]. The concerted action of the NCI and the GOG attracted a lot of media interest in the U.S. One can question this attention on the study of Armstrong et al. [3], because before that study a number of randomized studies on i.p. chemotherapy had already been published. Before the consensus meeting of the GCIG in 2005, seven studies on i.p. chemotherapy had already been published, of which six compared i.p. with i.v. chemotherapy in ovarian cancer [4–10].

GENERAL OBJECTIONS AGAINST THE USE OF I.P. CHEMOTHERAPY
Before elaborating on the randomized trials on i.p. chemotherapy in ovarian cancer, we raise some general objections on the use of i.p. treatment of ovarian cancer.

It has often been argued that the higher concentrations in the dialysate observed with the i.p. administration of cisplatin, compared with the i.v. administration of cisplatin, resulted in greater efficacy. However, one should not compare the i.p. dialysate concentration with the i.v. concentration of a drug, but rather the tumor concentration with both treatment modalities. It is well known that the higher tumor concentration observed with the i.p. administration of cisplatin only reaches to a depth of 1–2 mm. Furthermore, we know that the distribution of i.p. chemotherapy is limited because of the dense peritoneal connective tissue.

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Table 1. Randomized GOG phase III studies with i.p. chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>n of patients</th>
<th>Hazard ratio (overall survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG/GOG 104 [9]</td>
<td>Cisplatin, 100 mg/m² i.v.; cyclophosphamide, 600 mg/m² i.v.</td>
<td>546</td>
<td>0.72 (0.61–0.96); p = .02</td>
</tr>
<tr>
<td></td>
<td>Cisplatin, 100 mg/m² i.p.; cyclophosphamide, 600 mg/m² i.p.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 114/SWOG [10]</td>
<td>Cisplatin, 75 mg/m² i.v.; paclitaxel, 135 mg/m² 24-hr i.v.</td>
<td>462</td>
<td>0.81 (0.65–1.0); p = .05</td>
</tr>
<tr>
<td></td>
<td>Carboplatin, AUC 9 i.v. every 28 days × 2; cisplatin, 100 mg/m² i.p.; paclitaxel, 135 mg/m² 24-hr i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 172 [3]</td>
<td>Cisplatin, 75 mg/m² i.v.; paclitaxel, 135 mg/m² 24-hr i.v.</td>
<td>415</td>
<td>0.71 (0.58–0.97); p = .03</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel, 135 mg/m² 24-hr i.v.; cisplatin, 100 mg/m² i.p.; paclitaxel, 60 mg/m² i.p. on day 8</td>
<td></td>
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</tbody>
</table>

Abbreviations: AUC, area under the concentration–time curve; GOG, Gynecologic Oncology Group; SWOG, Southwest Oncology Group.
motherapy in the abdominal cavity is poor and that relapses often occur behind adhesions [11].

Finally, i.p. chemotherapy is recommended in patients with no residual tumor and without bowel resections. However, bowel resections are often needed in patients with stage III ovarian carcinoma optimally debulked to no residual tumor [3].

**Table 2. Reasons why the experimental i.p. arm in GOG 172 cannot be regarded as standard of care**

1. The significance for overall survival was only borderline ($p = .03$) and only a one-sided statistical test was performed.
2. The number of nonevaluable patients was higher than the absolute difference in survival.
3. For progression-free survival, the $p$-value (one-sided) was not significant.
4. The survival curves differ only after 15 months and this may be caused by second-line therapy.
5. The standard arm with paclitaxel and cisplatin has a substantially lower survival rate than the standard arms of other randomized trials in the same patient population.
6. More than half of the patients treated with i.p. chemotherapy were treated with i.v. chemotherapy (mostly paclitaxel plus carboplatin); paclitaxel plus carboplatin is less toxic than paclitaxel plus cisplatin (standard arm), and after paclitaxel plus carboplatin it is easier to administer second-line combination chemotherapy.
7. Only 42% of the patients could receive six cycles of i.p. chemotherapy.
8. i.p. chemotherapy resulted in significantly greater toxicity (bone marrow, gastrointestinal, neurological, etc.).
9. Quality of life was worse during the first year after i.p. chemotherapy than after i.v. chemotherapy.
10. In the experimental i.p. arm, a higher dose of cisplatin was administered and paclitaxel was administered both on day 1 and day 8; these differences might have influenced the survival results.
11. The number of i.p. versus retroperitoneal relapses was not different in the i.p. arm compared with the i.v. arm [12].

Abbreviation: GOG, Gynecologic Oncology Group.

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**ANALYSIS OF THE GOG TRIALS**

The three GOG trials are the most important trials on i.p. chemotherapy, and are summarized in Table 1. In the first study, the GOG and Southwestern Oncology Group (SWOG) randomized patients between i.v. cisplatin plus cyclophosphamide and i.p. cisplatin combined with i.v. cyclophosphamide [9]. After the publication of that trial, i.p. chemotherapy was not accepted as standard of care because at that time cisplatin plus cyclophosphamide was no longer the standard because cyclophosphamide had been replaced by paclitaxel. Furthermore, the morbidity was significantly greater in the i.p. group than in the i.v. group (e.g., only 58% of the patients in the i.p. arm received the planned six courses).

The second randomized GOG study was published by Markman et al. [10]. That study was criticized because the experimental arm differed in many ways from the standard arm. Indeed, in the experimental arm, the first two courses of carboplatin were administered at a high dose (AUC of 9), and the dosages of cisplatin were also different in the two arms. The toxicity was very high, and the authors concluded that i.p. chemotherapy as administered in their study could not be recommended as standard of care.

The third GOG study, GOG 172, published by Armstrong et al. [3], was the main reason given by the NCI for making their announcement. In the rest of this paper, we focus on the GOG 172 study. The main reasons why the experimental (i.p. chemotherapy) arm of the GOG 172 study cannot be regarded as standard of care are summarized in Table 2.

**REMARKS ON GOG 172**

For a more detailed analysis of the GOG 172 study we refer to our recent editorial published in the *Journal of Clinical Oncology* [13].

First, it should be noted that the difference in overall survival had a $p$-value of .03, which, although statistically significant, only just meets this criterion. However, this was not based on a true intention-to-treat analysis; 14 randomly assigned patients were not included in the survival calculation, with nearly twice as many of these excluded patients being assigned to i.p. treatment.

In addition, the authors performed a one-sided test, accepting that i.p. chemotherapy could not result in worse survival than with i.v. chemotherapy. It is obvious that before making the statistical analysis, one could not predict that i.p. chemotherapy would be better than i.v. chemotherapy. This is important, because it is known that a two-sided test would have resulted in a lower significance (i.e., probably nonsignificant). Furthermore, more patients in the experimental arm were lost to follow-up when compared with those treated in the control arm (11 versus five patients).

Another important topic is the fact that during the GCIG consensus meeting, progression-free survival was recommended as the primary endpoint for first-line randomized phase III trials, and not overall survival. The reason for this...
was that second-line treatments have been shown to improve overall survival (International Collaboration on Ovarian Neoplasms, ICON-4). This is important, because the difference with respect to progression-free survival in the GOG 172 study was even smaller than for overall survival, and failed significance ($p = .05$). Differences in the median progression-free survival time between control patients and those treated with i.p. therapy were 2.4 and 2.9 months for those with microscopic and macroscopic residual disease, respectively. Neither of these differences was statistically significant. In contrast, the differences in the median overall survival time were 12.5 months in patients without residual disease and 15.9 months in the entire population. Moreover, the main difference between the two arms of the trials occurred after progression. There are only two possible explanations for this observation. Either patients who relapsed after i.p. therapy live longer because the nature of the treatment has altered the biology of their disease or patients who relapse after i.p. therapy are able to receive more effective second-line treatment. In this respect, it is worth mentioning that the survival curves only started separating after 15 months. This is the time when most patients relapse and receive second-line chemotherapy. The exact second-line therapies used in the GOG 172 trial are not known. However, more patients in the i.p. arm received i.v. carboplatin, compared with the standard arm, in which more patients received i.v. cisplatin. It is well known that paclitaxel plus cisplatin results in more toxicity (e.g., neuropathy) than paclitaxel plus carboplatin. Because of this reason, single-agent second-line chemotherapy might have been used more often in the i.v. arm than in the i.p. arm. The toxicity of the i.p. chemotherapy used in the GOG 172 trial was very high (Figs. 1 and 2).

Finally, it is important to note that the administered doses of cisplatin (75 mg/m² versus 100 mg/m²) and paclitaxel (135 mg/m² on day 1 versus 135 mg/m² on day 1 and 60 mg/m² on day 8) are different. It has been shown that weekly paclitaxel is more efficient than 3-weekly paclitaxel in other diseases, such as breast cancer [14].

It has been observed that the half-life of cisplatin after i.p. administration is longer than after i.v. administration. This also might be a reason why survival was longer in the i.p. arm. However, one can question whether we should not investigate other schedules to increase the half-life of cisplatin that result in less toxicity than i.p. chemotherapy, for example, using continuous infusion or other platin analogues.

**CONCLUSION**

It can be concluded that, for the time being, we cannot offer an i.p. regimen that is both safer than and superior to the current standard of care, that is, i.v. paclitaxel plus carboplatin. Hence, women should not be subjected to i.p. chemotherapy outside the context of properly designed clinical trials. These trials must either assess i.p. therapy in comparison with the standard treatment or address the issue of route of administration for equivalent dosages and schedules of the same drugs, and not a mosaic of these questions. In addition, these trials should investigate i.p. regimens that are less toxic than the regimens used in the three GOG trials, and which can be combined with molecular targeted therapies.
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REFERENCES


