

## Three ongoing intraperitoneal chemotherapy trials in ovarian cancer

**Keiichi Fujiwara**

Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan

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The most significant characteristic feature of ovarian cancer is the intraperitoneal spread in its early occurrence. Therefore, it is reasonable to consider the intraperitoneal (IP) chemotherapy for this disease entity. The primary concept of IP chemotherapy is to expose the tumor tissue directly to an extremely high concentration of anticancer agents by perfusing inside the peritoneal cavity [1]. IP chemotherapy has been investigated for a long time, and there have actually been three large-scale randomized trials conducted in the US, all of which showed overall and/or progression-free survival benefit [2-4]. Based on these results, the National Cancer Institute (NCI) and the Gynecologic Oncology Group (GOG) performed a meta-analysis on the results of these three US trials and other phase III trials of IP versus intravenous (IV) chemotherapy, and significant improvement of survival was shown with IP therapy. Based on this meta-analysis, the NCI has released a clinical announcement encouraging the gynecological oncology community to consider IP chemotherapy using cisplatin as the standard treatment for advanced ovarian cancer patients in whom the residual disease were debulked to 1 cm or less [5]. Unfortunately, however, IP chemotherapy has not been adopted as a standard care because there are several controversial issues to be solved. One of the major issues to be resolved is the chemotherapy-related toxicity. Another concern is the catheter-related problems such as port infection or occlusion [4,6]. In the GOG 172 trial, the completion rate of IP

chemotherapy for 6 cycles was only 42%. Twenty-seven percent of them received either no IP chemotherapy (8%) or only one cycle (19%). Despite the fact that the majority of patients in the IP arm of the GOG 172 trial did not complete the IP chemotherapy, overall survival was significantly better than the IV chemotherapy arm. This raised the question of how many cycles of IP chemotherapy is needed to obtain survival advantage?

In this issue of the Journal, Kim et al. [7] reported the preliminary results of IP administration of cisplatin at the time of primary surgery followed by IV chemotherapy. The toxicities were acceptable as predicted, and the authors concluded that further prospective trials are warranted based on this study. The most advantageous benefit of this approach is that there is no need to place the access device for repeating IP chemotherapy. Also, as the authors described, the use of IP chemotherapy at the time of surgery and/or in the immediate postoperative period facilitates uniform drug delivery and may avoid some of the complications of prolonged peritoneal access.

However, it seems to be too early to test this approach in a large scale comparative trial, because we do not know how many cycles of IP chemotherapy is minimally needed to obtain survival advantage. In other words, only one cycle may lose the survival benefit of IP chemotherapy. In fact, it has not been elucidated why the GOG 172 trial demonstrated a strikingly better survival in the IP arm compared to the IV arm, despite the fact that many of the patients in the IP arm did not receive the complete IP regimen of chemotherapy [4]. Until we find some clues as to the background mechanisms involved in IP chemotherapy, we should try providing IP chemotherapy as many times as IV chemotherapy using IP access devices.

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Correspondence to Keiichi Fujiwara

Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan. Tel: 81-42-984-4637, Fax: 81-42-984-4741, E-mail: fujiwara@saitama-med.ac.jp

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The major drawback of IP chemotherapy is that the IP chemotherapy agent is cisplatin, which is more toxic and more difficult to manage compared to carboplatin, the current standard IV chemotherapy agent. Therefore, it is important to explore whether carboplatin may replace cisplatin in IP chemotherapy. Several studies have demonstrated that the use of carboplatin as IP chemotherapy would be feasible [8-10].

Currently, three large-scale randomized trials are ongoing to examine the efficacy of carboplatin-based IP chemotherapy. The simplest study is the iPocc Trial (GOTIC-001/JGOG-3019) [11]. In this trial, dose-dense weekly paclitaxel at 80 mg/m<sup>2</sup> will be administered in combination with carboplatin at area under the curve (AUC) 6 every three-week either by IV or IP. In this study, eligible patients are those with epithelial ovarian cancer stages II to IV, thus, this study will explore the potential of IP chemotherapy in suboptimally treated advanced ovarian cancer, and not only for optimally debulked cases.

The classical concept of IP chemotherapy is local therapy, which is the direct contact of cancer cells with anticancer drugs, and it is believed that direct penetration of agents is limited to a few millimeters from the tumor surface [1]. However, it has been hypothesized the carboplatin administered into the IP cavity is absorbed from the peritoneal surface within 24 hours and serum the AUC is exactly the same as serum platinum AUC after IV administration, although platinum AUC in the IP cavity was 17 times greater when carboplatin was given by the IP than the IV route [12]. It has been demonstrated that IP carboplatin for suboptimal residual cases was also feasible as a phase II trial [13], and therefore, the iPocc Trial is also challenging this important scientific question. The iPocc Trial has just been opened to international study groups such as the Korean Gynecologic Oncology Group (KGOG) or the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) of Austria. The contracts also have been under process with individual hospitals in Singapore, Australia, and Spain. The target accrual is 746, and at the present time approximately 100 patients have been enrolled, and the international community is encouraged to participate in this important trial.

Another trial is the GOG 252 study. In this trial, the control arm and one of the experimental arms are exactly the same as the iPocc Trial, except that there is a combination and maintenance administration of bevacizumab. The GOG incorporated this strategy based on the GOG 218 trial results. The GOG 252 trial has a third arm, which is the modified GOG 172 winner regimen. In this arm IV paclitaxel at 135 mg/m<sup>2</sup> on day 1 followed by IP cisplatin at 75 mg/m<sup>2</sup> on day 2, and then IP paclitaxel is administered on day 8. This arm also incorporates the combination and maintenance of bevacizumab. The GOG 252 trial has completed accrual and awaits for the results.

The third trial is the OV-21/GCIG study lead by the Canadian National Cancer Institute. This trial has a unique approach to the IP chemotherapy. All patients with stages III patients will receive neoadjuvant chemotherapy. Those patients who respond to the neoadjuvant chemotherapy will receive interval debulking surgery (IDS), and if the residual disease after IDS becomes the optimal <1 cm, the patient will be randomized to one of the three arms. The control arm is the combination of IV paclitaxel at 135 mg/m<sup>2</sup> followed by IV carboplatin at AUC 5 on day 1, and then IV paclitaxel at 60 mg/m<sup>2</sup> will be given on day 8. The second arm is same as the control arm but carboplatin will be given by the IP route. The third arm is the modified GOG 172 winner arm, which is the same as the third arm of GOG 252 trial but in which bevacizumab is not given. One of these two IP arms (arm 2 or arm 3) will be chosen, as a randomized phase II manner, and the winner arm will be compared with the control arm as phase the III trial.

These three trials have different patient populations and different treatment regimens, but will answer important questions when compared between trials. It is encouraged for gynecologic oncologists to participate in one of these trials to resolve the important IP chemotherapy questions for the future.

#### CONFLICT OF INTEREST

No potential conflict of interests relevant to this article was reported.

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