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H. 知的財産権の出願・登録状況（予定含）

なし

Int J Gynecol Cancer 2007, **17**, 1–20

REVIEW ARTICLES

Principles and practice of intraperitoneal chemotherapy for ovarian cancer

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Abstract. Fujiwara K, Armstrong D, Morgan M, Markman M. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. *Int J Gynecol Cancer* 2007;**17**:1–20.

Intraperitoneal (IP) chemotherapy has been studied for years to improve the survival of patients with ovarian cancer. Recently, the result of Gynecologic Oncology Group 172 trial comparing IP versus intravenous administration of cisplatin-based chemotherapy was published, demonstrating the improvement of survival benefit in favor of the IP arm. This trial is the third trial that showed a survival benefit on IP chemotherapy. The National Cancer Institute (NCI) and Gynecologic Oncology Group have done a meta-analysis on the results of these three US trials and other phase III trials of IP versus intravenous chemotherapy, and significant improvement of survival was shown with IP therapy. Based on this meta-analysis, NCI has released a clinical announcement encouraging the gynecological oncology community to consider IP chemotherapy as the standard treatment for optimally debulked advanced ovarian cancer patients. However, there still are controversial issues regarding the use of IP chemotherapy. It is important to understand how IP chemotherapy works to solve those issues in the future. In this review article, we discuss the principles and clinical aspects of IP chemotherapy and also discuss the current problems and future perspectives in IP chemotherapy.

KEYWORDS: intraperitoneal chemotherapy, ovarian cancer.

Introduction

Enormous effort has been made to improve the prognosis of epithelial ovarian cancer by conducting clinical trials in the recent few decades. Based on the results of a sequence of randomized phase III trials starting in the 1970s, the standard therapy for advanced ovarian cancer now is a maximum cytoreductive surgery followed by combination chemotherapy with paclitaxel and carboplatin[1]. Although some improvement in the survival has been shown, ovarian cancer still is the leading cause of death from gynecological malignancies in developed countries. Therefore, improvement in the therapeutic strategy in this disease is necessary.

One of the most characteristic features of ovarian cancer is the intraperitoneal (IP) spread of disease even in the early occurrence. Therefore, it has been considered reasonable to use IP delivery of chemotherapy in the treatment for ovarian cancer. This approach has been extensively investigated both preclinically and clinically.

IP chemotherapy was first adopted as palliative purposes to control ascites of various intra-abdominal malignancies in 1950s. Since 1978, IP chemotherapy has been started, having therapeutic intervention. A number of anticancer drugs have been tested in preclinical studies as well as in phase I and phase II trials. In late 1980s, South West Oncology Group (SWOG) and Gynecologic Oncology Group (GOG) have conducted the first randomized phase III trial comparing IP and intravenous (IV) cisplatin-based chemotherapy. A survival benefit in favor of IP arm was demonstrated and presented in 1996.

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doi:10.1111/j.1525-1438.2007.00809.x

Since then, two additional large randomized phase III studies also showed a survival benefit on IP chemotherapy. The National Cancer Institute (NCI) and GOG have done a meta-analysis on the results of these three US trials and other phase III trials of IP versus IV chemotherapy, and significant improvement of survival was shown with IP therapy. Based on this meta-analysis, NCI has released a clinical announcement encouraging the gynecological oncology community to consider IP chemotherapy as the standard treatment for optimally debulked advanced ovarian cancer patients. However, there still are controversial issues regarding the use of IP chemotherapy. It is important to understand how IP chemotherapy works to solve those issues in the future.

In this review article, we discuss the principles and clinical aspects of IP chemotherapy and also discuss the current problems and future perspectives in IP chemotherapy.

Principles of IP chemotherapy

Basic concept of IP chemotherapy

What is the ideal anticancer agent for IP chemotherapy?

The primary concept of IP chemotherapy is to directly expose the tumor tissue to an extremely high concentration of anticancer agent by perfusing inside the peritoneal cavity. As shown in the Figure 1, however, some proportion of anticancer agent infused into peritoneal cavity will go into the capillary blood vessels adjacent to the peritoneum and systemic circulation, and then return to the inner core of tumor tissue through tumor microcirculation. Drug concentration of the inner core of the tumor depends on the drug pharmacokinetics. Therefore, factors that determine the effect of IP chemotherapy are (1) direct penetration of anticancer agent into the tumor tissue from tumor surface, (2) diffusion of anticancer agent into inner core of tumor tissue through systemic blood circulation, and most importantly (3) antitumor effect of the agent for ovarian cancer.

Based on these determinant factors, an ideal anticancer agent for IP chemotherapy is the one that is very effective systemically against ovarian cancer, penetrates deep into the tumor, and stays in the peritoneal cavity for prolonged periods as a low incidence of systemic adverse effects while providing satisfactory drug concentrations in the inner core of tumor tissue. However, things are not that easy.

Penetration of anticancer agents

A number of preclinical experiments have been performed for variety of anticancer agents. Fundamentally, penetration of anticancer drugs from the tumor surface is limited to a few millimeters.

Doxorubicin. Ozols *et al.* first reported that intraperitoneally administered doxorubicin penetrated only into the outermost four to six cell layers of intra-abdominal murine ovarian cancer tumors[2]. Durand also investigated the penetration of doxorubicin using spheroid model[3]. A marked gradient of doxorubicin uptake in cells of spheroids has been demonstrated by fluorescence photomicroscopy and flow microfluorometry techniques.

Methotrexate. West *et al.* evaluated the ability of methotrexate to penetrate solid tumor masses using human

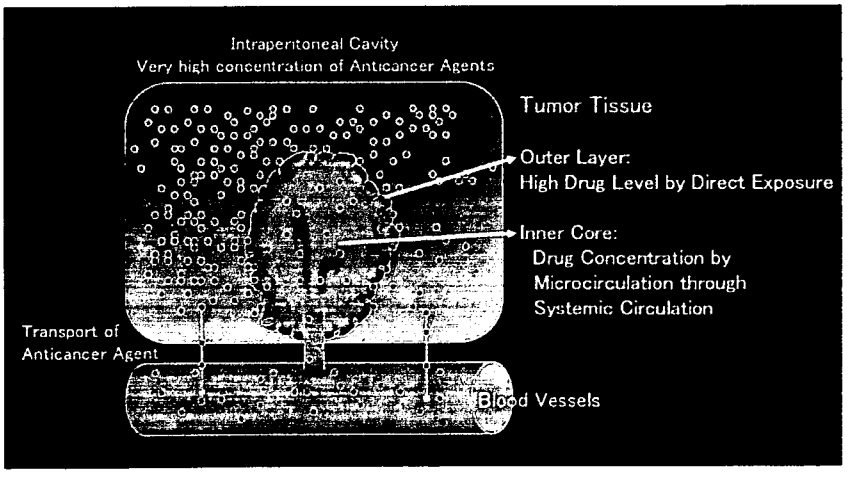

Figure 1. Basic pharmacologic concept of IP chemotherapy.

osteosarcoma spheroids[4]. Autoradiographs obtained from sections through the center of spheroids of various sizes suggested that methotrexate has a limited ability to penetrate into avascular tumor masses particularly when the tumor masses are approximately 250 μm and larger in diameter.

Vinblastine and 5-fluorouracil. Nederman and Carlsson reported a penetration study for vinblastine and 5-fluorouracil (5-FU) in 1984[5]. The penetration of radiolabeled drugs was measured in glioma spheroids, and they found that vinblastine penetrated the spheroids less efficiently than 5-FU.

Cisplatin. Los *et al.* reported the penetration of cisplatin in a rat IP tumor model in 1989[6]. Although the platinum concentration in the IP tumor nodules was always higher after IP treatment than after IV treatment, platinum concentrations were higher at the periphery of the tumor after IP administration than after IV infusion. On the other hand platinum concentrations in the center of the tumor nodules were identical.

Peritoneal dwelling of anticancer drug

Pharmacologically, longer stay of anticancer agents after IP administration and higher drug concentration in the inner core of tumor tissue is contrary phenomenon. In other words, the agents that stay longer in the peritoneal cavity go into systemic circulation slowly, and consequently, it can achieve less drug concentration in the inner core of the tumor (see Solute Transport Model for IP Chemotherapy section for detailed mechanism).

Among a number of anticancer drugs investigated for ovarian cancer, the most effective anticancer agents are platinum compounds, such as cisplatin or carboplatin. Unfortunately, platinum agents are not pharmacologically optimal for IP chemotherapy (see Theoretical Peritoneal Dwelling of Drugs in the Peritoneal Cavity).

Solute transport model for IP chemotherapy

Solute transport system has been extensively investigated in the peritoneal dialysis area. It is important to be familiar with the anatomy of the peritoneum and adjacent tissue to understand how anticancer agents administered into the IP cavity behave.

Anatomy of the peritoneum and capillary vessels

Peritoneum. The peritoneal membrane is the primary interface between abdominal cavity and blood vessels. The peritoneal membrane is composed of two principal parts: (1) the parietal peritoneum and (2) visceral peritoneum. The parietal peritoneum is about 10% of total peritoneal area and covers the inner surface of the abdomen, diaphragm, and pelvic wall. The visceral peritoneum is about 90% of total and covers the visceral organs such as the intra-abdominal portion of the gastrointestinal tract, the liver, and the spleen, and forms the omentum and visceral mesentery. The total surface area of the peritoneal membrane in the adults is believed to approximate the body surface area (1.0–2.0 m^2). Important anatomic components of the peritoneal membrane from the perspective of IP chemotherapy are the mesothelium, the underlying basement membrane, the interstitium, microcirculation, and the visceral lymphatics.

Mesothelium. The mesothelium is a continuous monolayer of flattened cells about 0.5-mm thick. The cells have tortuous boundaries having several types of function that allow for adhesion and communication between cells. The tight junctions have an anchoring function that mechanically attaches cells to one another and to the basement membrane. The gap junctions mediate the passage of chemical or electrical signals. The antiluminal surface has many open intracellular channels approximately 50 nm wide. The absence of tight junction in the subdiaphragmatic region results in the formation of stomas that allow direct contact between the peritoneal cavity and the diaphragmatic lymphatics. Therefore, peritoneal fluid and its solutes are directly absorbed into the lymphatic system through the subdiaphragmatic stoma.

Interstitium. The interstitium is the supporting structure of the peritoneum. It contains bundles of collagen fibers, blood vessels, and the lymphatics. The distance between capillaries and the mesothelial surface varies.

Blood vessels. The blood supplies to the visceral and parietal membranes are defined as two different sources. The visceral peritoneal membrane is supplied by the celiac and mesenteric arteries with venous drainage via the portal vein. Therefore, any IP-administered drug from the visceral peritoneum, which is about 90% of total peritoneal surface, results in rapid first-pass metabolism by the liver. The parietal mesothelium is supplied by the circumflex iliac, lumbar, intercostal, and epigastric arteries with venous drainage directly into the systemic circulation, bypassing the hepatic portal system. Solute transport is influenced by the density of the number of perfused capillaries, which is called effective peritoneal surface area. Therefore, the larger the proportion of peritoneal adhesion is, the less solute transport will be. Solute

transport is also influenced by the number and size of pores within the capillaries.

Peritoneal lymphatics. The lymphatic network is extensively developed in the subdiaphragmatic area, where stomas exist. Since the basement membrane is absent in these areas, there is little resistance for the solute transport. Lymphatics are also present in the parietal mesothelium as well as in the submucosal layers of most of the visceral mesothelium. The lymphatic vessels function to maintain the relatively small volume of fluid (50–100 mL).

Resistance to solute transport

The exact route taken by solutes as they pass from peritoneal cavity into blood vessels has not been well established. It is supposed that potential resistance sites of solute transport include (1) fluid films within the peritoneal cavity, (2) the mesothelial layer (0.9 mm), (3) the interstitium (0.1–100 mm), (4) the capillary basement membrane (0.2–5 mm), (5) the endothelial layer (0.5 μm), and (6) fluid films within the capillary lumen. Among these resistance, fluid films are believed to exert little resistance because of the very short distance.

The schema illustrating resistance other than water films is shown in Figure 2. Among those resistances, endothelium appears to be the key component that determines the permeability of large molecules such as anticancer agents. The mesothelium is believed to be more permeable than the endothelium, possibly because the intercellular gaps are larger. Although the interstitium represents the longest distance that solutes must transverse and it is the major resistance sites for urea and low-molecular weight solute transport, transport of larger molecules has not been well defined and further research is needed[7]. Transport of solute across the capillary endothelium is defined as three-pore model that consists of water channel, small pores, and large pores[8] (Fig. 2). Water channels representing about 1–2% of the total pore number and having a radius smaller than 0.8 nm permit only water to pass. Small pores are the interendothelial clefts with a radius smaller than 4–6 nm representing 90–93% of the total pore number. These pores tend to be located along the arteriolar end of capillaries and severely restrict the passage of larger molecules such as protein. They allow small molecules to flow freely. Large pores, with radii larger than 20 nm, are located in the venular side of capillaries and account for 5–7% of the overall pore area. These pores allow macromolecules and water through hydrostatic forces.

Theoretical peritoneal dwelling of drugs in the peritoneal cavity

Based on the anatomic characteristics, theoretical behavior of anticancer agents is summarized as follows.

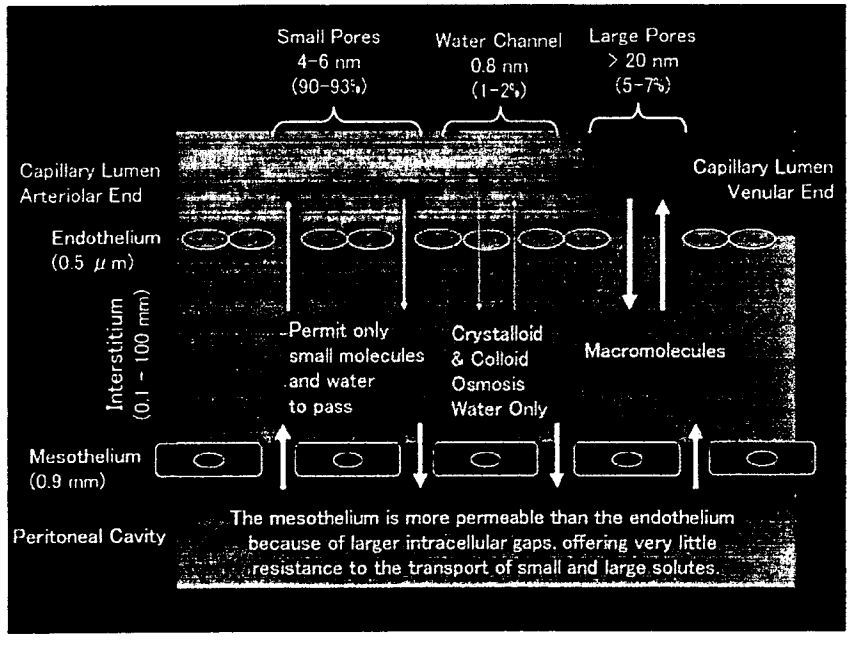

Figure 2. Mechanism of solute transport between peritoneal cavity and capillary lumen (adopted and modified with permission from Burkart *et al.*[8]).

1. Larger molecular weight or water-insoluble anticancer drugs stay longer in the peritoneal cavity, and the (peritoneal cavity/plasma) drug ratio is larger. Therefore, these drugs do not go into the inner core of the tumor tissue.
2. Smaller molecular weight or water-soluble anticancer drugs stay shorter in the peritoneal cavity, and (peritoneal cavity/plasma) drug ratio is smaller. Therefore, these drugs can go into the inner core of the tumor tissue easily but stay in the IP cavity for a shorter time.
3. Small molecular weight agents that are metabolized in the liver to become active forms should not be used for IP chemotherapy because they are not active in the IP cavity, and most drug molecules are drained into systemic circulation as active forms through portal vein.
4. On the other hand, small molecular weight agents that are already active forms are suitable for IP chemotherapy because they are metabolized in the liver through portal vein, and systemic adverse effect is reduced while exposing IP tumor with high concentration.

Table 1 shows the list of anticancer agents for IP chemotherapy and their molecular weight, water solubility, and (peritoneal cavity/plasma) ratio of drug levels. As shown in the Table 1, larger molecular weight and water insolubility correlate well with a larger peritoneal/plasma ratio. As for those agents showing larger peritoneal/plasma ratio in spite of smaller molecular weight and good water solubility, such as 5-FU, it is suggested that those agents are metabolized in the liver through portal vein.

Since penetration of anticancer agents from tumor surface is limited, the indication for IP chemotherapy should be limited to the small residual disease, if the IP chemotherapy is considered to be a regional therapy in the peritoneal cavity. In this setting, the ideal chemotherapy agents are large molecules such as paclitaxel or mitoxantrone. As shown in this table, platinum agents, which are most effective against ovarian cancer, do not stay long in the peritoneal cavity; therefore, these are not suitable for the "genuine" IP chemotherapy. However, these agents can easily go into systemic circulation and ultimately reach the inner core of tumor tissue. Therefore, IP chemotherapy using platinum agents can be hypothesized as one route of systemic chemotherapy.

Pharmacology of IP chemotherapy

Table 2 summarizes results of phase I trials with or without pharmacokinetic study[9–26]. Among those agents, this section will discuss the pharmacology of IP cisplatin, carboplatin, and paclitaxel including animal experiments.

Cisplatin

Howell *et al.* reported pharmacokinetics of IP cisplatin administration[27]. They reported that the peak peritoneal concentration of free reactive cisplatin was approximately 21-fold higher than the plasma level, and the area under curve (AUC) of cisplatin was 12-fold more than the area under the plasma curve. Pretorius *et al.* compared the pharmacology and toxicity of cisplatin following IP or IV administration in dogs[28]. They found that the mode of administration did not affect systemic toxicity since the changes in renal and bone marrow functions were identical in the two groups. Although peak serum cisplatin levels were higher following IV administration (13.5 mcg/

Table 1. Pharmacologic advantage for IP chemotherapy

			Ratio of drug level, peritoneal cavity/plasma	
Drug	Molecular weight	Water solubility	Peak	AUC
Cisplatin	300.05	+	20	12
Carboplatin	371.25	+	24	10–18
Topotecan	457.91	+		54
Mitomycin	334.33	±	71	—
Melphalan	305.20	—	93	65
Methotrexate	454.44	—	92	100
Docetaxel	861.94	—		181
5-FU	130.08	±	298	367
Doxorubicin	543.53	±	474	—
Gemcitabine	299.66	+		759
Paclitaxel	853.92	—	—	1000
Mitoxantrone	517.40	—	—	1400

Adopted and modified from Markman M. *Semin Oncol* 1991;18:248–54.

mL) compared with the levels following IP administration (1.5 mcg/mL), the amount of drug recovered in the urine was similar regardless of method of administration, with approximately 50% of the injected dose excreted by day 4. The drug levels within the tissues were similar, with the exception of the tissues lining the peritoneal cavity. The peritoneal lining had 2.5–8 times higher levels of drug after IP administration. They suggested that IP cisplatin chemotherapy might increase the therapeutic index for small tumors confined to the peritoneal cavity.

Carboplatin

Elferink *et al.* reported the pharmacokinetic study of IP carboplatin administration in 1998[29]. In this study, the peritoneal fluid was withdrawn after a 4-h dwell. The mean ratio of peak concentrations of carboplatin in instilled fluid and plasma was 24 ± 11, and the AUCs for the peritoneal cavity were about ten times higher than those for plasma. Recently, Miyagi *et al.* published a comparative pharmacologic study after IP and IV carboplatin[30]. In this study, they tried to clarify the pharmacologic advantage of carboplatin-based IP chemotherapy using the three-compartment mathematical model. They administered carboplatin at AUC = 6 either IP or IV, and then collected IP fluid and blood samples. The mathematical model consisting of a three-compartment model was applied to analyze the pharmacokinetics. The model was created with simultaneous differential equations and was solved by the Runge-Kutta method. By using this model, the theoretical pharmacologic concentration of platinum, 24-h free platinum AUC in the serum, was identical regardless of IP or IV administration of carboplatin.

Table 2. Phase I trials for IP chemotherapy

	Reference	Year	IP agent	Maximum tolerable dose	Dose-limiting toxicity	Peritoneal/plasma ratio
1	Alberts *et al.*[9]	1988	Mitoxiantrone	38 mg/m^2	Leukopenia, abdominal pain	1408 (AUC)
2	Blochl-Daum *et al.*[10]	1988	Mitoxiantrone	30 mg/m^2	Leukopenia	1109 (AUC)
3	DeGregorio *et al.*[11]	1986	Carboplatin			18 (AUC)
4	Francis *et al.*[12]	1995	Paclitaxel	60–65 mg/m^2/week	Abdominal pain, nausea, vomiting, leukopenia, fatigue	
5	Hofstra *et al.*[13]	2001	Topotecan	20 mg/m^2	Acute hypotension, chills and fever	54 (AUC)
6	Isonishi *et al.*[14]	1991	Etoposide, dipyridamole	175 mg/m^2/day, 24 mg/m^2/day, for 3 days	Leukopenia, thrombocytopenia	
7	Kirmani *et al.*[15]	1990	Thiotepa	60 mg/m^2	Myelosuppression	
8	Malmstrom *et al.*[16]	1990	Carboplatin	500 mg/m^2	Thrombocytopenia, leukocytopenia	
9	Markman *et al.*[17]	1992	Paclitaxel	175 mg/m^2/day	Abdominal pain	1000 (AUC)
10	McClay *et al.*[18]	1993	Carboplatin, etoposide	300 mg/m^2, 350 mg/m^2	Neutropenia	
11	McClay *et al.*[19]	1994	Carboplatin, etoposide[a]	600 mg/m^2, 400 mg/m^2, for 3 days	Hematologic	
12	Morgan *et al.*[20]	2003	Docetaxel	100 mg/m^2	Neutropenic sepsis, stomatitis	181 (AUC)
13	Muggia *et al.*[21]	1991	Floxuridine	3000 mg/body/days, for 3 days		2 to 4 log pharmacologic advantage
14	Oza *et al.*[22]	1994	Mitoxiantrone	25 mg/m^2	Leukocytopenia, peritoneal irritation and pain	
15	Plaxe *et al.*[23]	1998	Topotecan	4 mg/m^2	Neutropenia	31.2 (AUC)
16	Sabbatini *et al.*[24]	2004	Cisplatin, gemcitabine	75 mg/m^2 (fixed)		759 (AUC) for gemcitabine
17	Speyer *et al.*[25]	1980	5-FU	4.5–5 mM	Mucositis, pancytopenia	298 (peak)
18	Zimm *et al.*[26]	1987	Cisplatin, etoposide	200 mg/m^2 (fixed), 350 mg/m^2		65 (etoposide)

[a]Granulocyte macrophage colony stimulating factor (GM-CSF) 500 mcg/m^2/day was mandatory.

However, the 24-h platinum AUC in the peritoneal cavity was approximately 17 times higher when carboplatin was administered by the IP route. This study suggested that IP infusion of carboplatin is feasible not only as an IP regional therapy but also as a more reasonable route for systemic chemotherapy. In the phase I/II trial conducted by Speyer and Sorich in 1992, the recommended dose of IP carboplatin was 400 mg/m^2[31].

Paclitaxel

Markman *et al.* published the first phase I study for IP paclitaxel in 1992[17]. The dose-limiting toxicity of IP paclitaxel was severe abdominal pain at the doses more than 175 mg/m^2. Moderate leukopenia was observed at IP doses of greater than or equal to 175 mg/m^2. The exposure of the peritoneal cavity (peak levels and AUC) to paclitaxel after IP delivery exceeded that of the plasma by approximately 1000-fold. Significant concentrations of paclitaxel persisted within the peritoneal cavity for more than 24–48 h after a single IP installation.

Francis *et al.* subsequently reported a phase I study of weekly administration of IP paclitaxel in patients with residual ovarian cancer after standard chemotherapy and found that recommended dose for phase II study was 60–65 mg/m^2 weekly[12]. At dose levels $\geq$ 60 mg/m^2, the persistence of significant levels of paclitaxel in the IP cavity 1 week after drug administration suggests the very slow peritoneal clearance. Consequently low plasma paclitaxel concentrations were detected in the majority of patients treated at dose levels $\geq$55 mg/m^2.

Clinical aspects of IP chemotherapy

In this section, we discuss the clinical aspect of IP chemotherapy including phase II and III trial results, IP catheter issue, and future directions.

Phase II trials

A number of phase II trials have been reported regarding IP chemotherapy for ovarian cancer as summarized in Table 3[32–50]. However, it is difficult to compare the efficacy of those agents in these phase II studies because the choice of patient population is different. For example, most studies have been performed in a salvage setting for patients with minimal residual disease at the second-look laparotomy after front-line chemotherapy or those with recurrent disease, but the definition of minimal residual disease varied as the maximum diameter of 0.5, 1, or 2 cm. Moreover, some studies tested single agents, but other studies tested combination. Endpoints also varied. Some studies evaluated response rates radiographically or with second-look laparotomies, and the others evaluated progression-free or overall survival.

Among those agents, three most important agents, cisplatin, carboplatin, and paclitaxel, and the combination of cisplatin and paclitaxel will be highlighted.

IP cisplatin was tested either alone or in combination with etoposide, 5-FU, paclitaxel or others. Guastalla *et al.* tested the efficacy of IP cisplatin at 90 mg/m^2. In 25 evaluable cases, response rate was 16% including three pathologic complete response (CR)[36]. Guastalla *et al.* also tested the efficacy of IP carboplatin at 300 mg/m^2 for patients with macroscopic residual disease at second-look laparotomy after cisplatin first-line treatment[37]. Although they concluded that IP carboplatin is not recommended for phase III trial because of the low response rate of 12%, we believe that this response rate is reasonable because the patients were cisplatin resistant and the dose of carboplatin was relatively lower. IP carboplatin at 500 mg/m^2 was tested as adjuvant therapy for stage I and II ovarian cancer patients[16], and recurrent rate was 23%. Markman *et al.* published efficacy and toxicities of IP administration of paclitaxel at 60 mg/m^2 weekly for 16 weeks in 80 patients with small residual disease ($\leq$0.5 cm) at second-look laparotomy[43]. Surgical complete response was observed in 61% of patients with microscopic disease, but it was observed only in 3% of patients with macroscopic disease.

IP cisplatin or IP carboplatin was also tested in combination with other IP or IV agents (Table 3). Among those studies, combination of IP cisplatin and IV or IP paclitaxel seems to be important. Rothenberg *et al.* reported in 2003 the phase II study of combination of treatment with paclitaxel 135 mg/m^2 IV over 24 h on day 1, cisplatin 100 mg/m^2 IP on day 2, and paclitaxel 60 mg/m^2 IP on day 8 administered every 21 days for six cycles[49]. In 68 assessable women with optimal stage III ovarian cancer, the 2-year survival rate was 91%, and the median survival time was 51 months. The 2-year disease-free survival rate was 66%, and median disease-free survival time was 33 months. At least one grade 3 to 4 adverse event was observed in 96% of all patients during therapy, with the most common events being neutropenia (79%), nausea (50%), vomiting (34%), and fatigue/malaise/lethargy (24%). Seventy-one percent of patients completed all six cycles. This study lead to the GOG 172 phase III randomized trial.

Table 3. Phase II trials of IP chemotherapy

	Reference	Year	IP agent, dose	IV agent, dose	Study setting	Patient number	Efficacy	Toxicities
1	Barakat *et al.*[32]	1998	Cisplatin 100 mg/m^2, etoposide 200 mg/m^2	—	Consolidation, pathologically negative at SLL	40	Median FU 36 months, recurrent rate 39% (IP), recurrent rate 54% (control)	
2	Braly *et al.*[33]	1995	Cisplatin 100 mg/m^2, 5-FU 2000 mg	—	Salvage residual <1 cm at SLL or recurrent	45. Cisplatin sensitive 13; cisplatin refractory 32	No progression 22; surgical assessment 15; 3 pCR; 3 PR (all sensitive)	WBC nadir 2800; PLT nadir 12,200
3	de Jong *et al.*[34]	1995	Cisplatin 90 mg/m^2 (day 1)	Etoposide 600–800 mg/m^2 (days 1 and 2)	Salvage for residual <2 cm after first line	36	7 pCR; 1 pPR; 16 SD; median PFS 11 months; PFS at 24 months: 22%	G3/4 ANC 63%; G3/4 PLT 8%
4	Feun *et al.*[35]	1998	Cisplatin 100 mg/m^2, thiotepa 30 mg/m^2	—	Salvage residual <0.5 cm after first-line chemotherapy at SLL	65 (52 Evaluable), 16 patients surgical assessment	19% CR; 2% PR; 10 patients surgical CR; one patient surgical PR	
5	Guastalla *et al.*[36]	1994	Cisplatin 90 mg/m^2 (60 mg/m^2 first cycle)	With sodium thiosulfate protection	Salvage residual <1 cm	34 (25 evaluable)	3 pCR, RR = 16%	2 patients peritonitis; 9 partial catheter obstruction; 1 complete catheter obstruction
6	Guastalla *et al.*[37]	1994	Carboplatin 300 mg/m^2	—	Salvage macroscopic residual at SLL after cisplatin first line	29	RR = 12% (2 pCR/29); concluded that IP carboplatin is not recommended for randomized phase III trial	0 peritoneal complications; 1 catheter obstructions; 0 grade 4 Hematologic Toxicity
7	Howell *et al.*[38]	1990	Cisplatin 200 mg/m^2, etoposide 300 mg/m^2	With sodium thiosulfate protection	Front-line, stage III/IV any size	23	56% CR (13/23); in 7 patients with SLL; 3 (13%) pCR; 4 (17%) microresidual; 27-month survival = 68%	Median nadir, WBC 2600; ANC 896; PLT 205,000; neurotoxicity, similar to IV cisplatin
8	Husain *et al.*[39]	1999	Cisplatin 100 mg/m^2, mitoxantrone 10 mg/m^2	—	Salvage for small residual at SLL	42	PFS 22.5 months; OS 47 (6–72) months	12 patients, catheter problems
9	Kirmani *et al.*[40]	1991	Cisplatin 200 mg/m^2, etoposide 350 mg/m^2	With sodium thiosulfate protection	Salvage for relapsed or persistent <2 cm	37	OS 26 months	WBC nadir 2400; ANC nadir 684; PLT nadir 13,400
10	Malmstrom *et al.*[41]	1994	Carboplatin 500 mg/m^2	—	Adjuvant, 31 stage I; 16 stage II	47	Recurrent rate 23% (10)	IP problems: more in relapsed patients; G4 WBC 6.7%; G4 PLT 17.8%
11	Markman *et al.*[42]	1990	Mitoxantrone 30 mg/m^2	—	Salvage	31	Surgically documented response 33% (6/18) in tumor ≤ 1 cm; 9% (1/9) in tumor > 1 cm	Abdominal pain requiring narcotics (>74%); 4 bowel obstruction; 2 intra-abdominal abscess

Continued

Table 3. Continued

	Reference	Year	IP agent, dose	IV agent, dose	Study setting	Patient number	Efficacy	Toxicities
12	Markman *et al.*[43]	1998	Paclitaxel 60 mg/m^2 weekly for 16 weeks	—	Salvage for small residual (≤0.5 cm) at SLL	80, 76 eligible	Surgical CR 61% (17/28) in patients with microscopic disease; 3% (1/31) in patients with macroscopic disease	Moderate abdominal pain grade 2, 12 patients; grade 3, 1 patient; minimal neutropenia, grade 2, 3 patients; grade 3, 1 patient
13	Markman *et al.*[44]	1991	Mitoxantrone 20 mg/m^2 weekly or biweekly	—	Salvage to previous cisplatin	28	31% (4/13 assessable patients)	Less toxicities compared to monthly regimen with 20 mg/m^2
14	McClay *et al.*[45]	1995	Carboplatin 600 mg/m^2, etoposide 400 mg/m^2, over 3 days	—	Salvage for the refractory to conventional modes of therapy	18	69% (9/13) response (majority is CA125 response)	Formidable 78% removed from protocol treatment
15	Morgan *et al.*[46]	2000	Cisplatin 90 mg or less; 5-FU 1040 mg 4-h dwell	—	Salvage to 9 residual; 5 progression; 10 recurrent	24	27% response (2/9) (1 CR, 1 PR); median PFS 7.0 (0.5–137) months; median OS 15.5 (3–147) months	Hypomagnesemia, vomiting, abdominal pain, mild anemia. 1 renal for dose reduction
16	Morgan *et al.*[47]	1999	Cisplatin 90 mg/m^2 4-h dwell	Doxorubicin 50 mg/m^2; cyclophosphamide 500 mg/m^2	Front line	43 (3 IC, 5 IIC, 14 optimal III, 14 suboptimal III, 7 IV)	6 in 8 stage IC, II patients disease free 12 years, 7 CR, 3 PR in 14 optimal III, 4 CR 4 PR in suboptimal III, 5-year PFS 21%, 5-year OS 64%	Neutropenia (sepsis 2 patients); mild anemia; renal 38% requiring dose reduction
17	Muggia *et al.*[48]	1996	Mitoxantrone 10 mg/m^2 biweekly or floxuridine 3 g/day for 3 days	—	Randomized phase II, Salvage to small residual (≤1 cm) at SLL	83 registered; 67 evaluable (39 mitoxantrone, 28 floxuridine)	Median PFS: mitoxantrone 11; floxuridine 25; median OS: mitoxantrone 21; floxuridine 38	
18	Rothenberg *et al.*[49]	2003	Cisplatin 100 mg/m^2 day 2; paclitaxel 60 mg/m^2 day 8	Paclitaxel	Front-line stage III optimal	68 assessable	2-year DFS 66%, OS 91%, median DFS 33 months, OS 51 months	96% patients with adverse events; neutropenia 79%; nausea 50%; vomiting 34%; fatigue 24%; 71% completed 6 cycles
19	Sood *et al.*[50]	2004	Topotecan 1 mg/m^2 days 1–5	Oral etoposide	Salvage for platinum resistant	22	ORR 38% (14% CR, 24% PR)	Grade 4 neutropenia 36%; grade 4 thrombocytopenia 18%

SLL, second look laparotomy; FU, follow-up; WBC, white blood cell; PLT, platelet; pCR, pathological complete response; PR, partial response; PFS, progression-free survival; ANC, absolute neutrophil count; CR, complete response; RR, response rate; OS, overall survival; DFS, disease-free survival; ORR, overall response rate.

Table 4. Randomized phase III trials comparing IV versus IP/IV first-line treatment of ovarian cancer

Study identifier/year published	Control regimen	Experimental regimen	Eligible patients	Number of patients	Median survival of control regimen (months)	Median survival of experimental regimen (months)
Kirmani *et al.*, 1994[51]	Cisplatin 100 mg/m^2 IV; cyclophosphamide 600 mg/m^2; q 3 weeks × 6	Cisplatin 200 mg/m^2 IP; etoposide 350 mg/m^2 IP; q 4 weeks × 6	Stage IIC-IV	62	Not mentioned; median PFS 14 months	Not mentioned; median PFS 12 months; NS
SWOG 8501/GOG 104; Alberts *et al.*, 1996[58]	Cisplatin 100 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV; q 3 weeks × 6	Cisplatin 100 mg/m^2 IP; cyclophosphamide 600 mg/m^2 IV; q 3 weeks × 6	Stage III, ≤2 cm residual	546	41	49; $P = 0.02$
Polyzos *et al.*, 1999[52]	Carboplatin 350 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV; q 3 weeks × 6	Carboplatin 350 mg/m^2 IP; cyclophosphamide 600 mg/ m^2 IV; q 3 weeks × 6	Stage III	90	52	63; NS
Gadducci *et al.*, 2000[53]	Cisplatin 50 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV; epidoxorubicin 60 mg/m^2 IV; q 4 weeks × 6	Cisplatin 50 mg/m^2 IP; cyclophosphamide 600 mg/ m^2 IV; epidoxorubicin 60 mg/m^2 IV; q 4 weeks × 6	Stage II–IV, <2 cm residual	113	25	26; NS
GOG 114/SWOG 9227; Markman *et al.*, 2001[54]	Cisplatin 75 mg/m^2 IV; paclitaxel 135 mg/m^2 (24 h) IV; q 3 weeks × 6	Carboplatin (AUC9) IV q 28 days × 2; cisplatin 100 mg/ m^2 IP; paclitaxel 135 mg/m^2 (24 h) IV q 3 weeks × 6	Stage III, ≤1 cm residual	462	51	67; $P = 0.05$
Yen *et al.*, 2001[55]	Cisplatin 50 mg/m^2 IV; cyclophosphamide 50 mg/m^2 IV; epidoxorubicin/doxorubicin 50 mg/m^2 IV; q 3 weeks × 6	Cisplatin 100 mg/m^2 IP; cyclophosphamide 500 mg/m^2 IV; epidoxorubicin/ doxorubicin 50 mg/m^2 IV; q 3 weeks × 6	Stage III, ≤1 cm residual	118	48	43; NS
GOG 172; Armstrong *et al.*, 2006[57]	Cisplatin 75 mg/m^2 IV; paclitaxel 135 mg/m^2 (24 h) IV; q 3 weeks × 6	Paclitaxel 135 mg/m^2 (24 h) IV; cisplatin 100 mg/m^2 IP; paclitaxel 60 mg/m^2 IP on day 8; q 3 weeks × 6	Stage III, ≤1 cm residual	415	49	67; $P = 0.03$

Continued

Table 4. Continued

Study identifier/year published	Control regimen	Experimental regimen	Eligible patients	Number of patients	Median survival of control regimen (months)	Median survival of experimental regimen (months)
Consolidation study EORTC-55875; Piccart *et al.*, 2003[25]	Surveillance	Cisplatin 100 mg/m^2 IP, Q 3 weeks × 4	Stage IIB–III in pCR following platinum-based primary treatment	153	78	91; NS
—[a]					IV Cisplatin arm	IV Carboplatin arm
GOG 158				792	49	57

[a]Survival data of GOG 158 trial are also listed as a reference.
NS, not significant; PFS, progression-free survival; pCR, pathological complete response.

Phase III trials of IP versus IV cisplatin-based chemotherapy

There are eight published comparative studies of IP versus IV administration for ovarian cancer as listed in Table 4[51–57] (all of these trials except EORTC 55875 were for the front-line therapy. EORTC 55875 was for no further treatment or for the consolidation with IP therapy after primary surgery and adjuvant chemotherapy). NCI US and GOG have conducted a meta-analysis of these eight trials and concluded that IP chemotherapy is beneficial for optimally debulked stage III ovarian cancer patients. Median survival reported for the control and experimental (IP) arms for the eight trials is shown in Table 4. The estimated treatment hazard ratios for progression-free survival, based on available data, are shown in Figure 3. The estimated relative death rates are displayed in Figure 4 for six of the eight studies (the relative death rate was not reported in the studies by Kirmani *et al.* and Polyzos *et al.*[52]). On average, IP therapy was associated with a 21.6% decrease in the risk of death (hazard ratio = 0.79; 95% confidence interval [CI] 0.70–0.89). The expected median duration of survival for women with optimally debulked ovarian cancer receiving standard treatment is approximately 4 years. Therefore, this size reduction in the overall death rate is expected to translate into about a 12-month increase in overall median survival. This important information has been released as a clinical announcement from NCI US in January 2006 (http://ctep.cancer.gov/highlights/ovarian.html).

Among those randomized trials in the meta-analysis, three most important trials, in terms of size of trials, conducted in the US cooperative trial groups will be further discussed in this section.

The first randomized trial conducted by SWOG and GOG 104 was published in 1996[58]. In this trial, patients with small residual disease (<2 cm) were randomized to receive six cycles of IV cyclophosphamide (600 mg/m^2) plus either IP or IV cisplatin (Fig. 5). The dose of cisplatin was 100 mg/m^2 for both groups, and the treatment was repeated every 3 weeks for six cycles. In the 546 eligible patients, the estimated median survival was significantly longer in the IP group (49 months; 95% CI 42–56) compared to the IV group (41 months; 95% CI 34–47). The hazard ratio for the risk of death was 0.76 (95% CI 0.61–0.96; $P = 0.02$) in favor of IP therapy (Fig. 6). Although moderate to severe abdominal pain was more frequent in the IP group, grade 3/4 granulocytopenia and tinnitus, clinical hearing loss, and grade 2–4 neuromuscular toxic effects were significantly more frequent in the IV group.

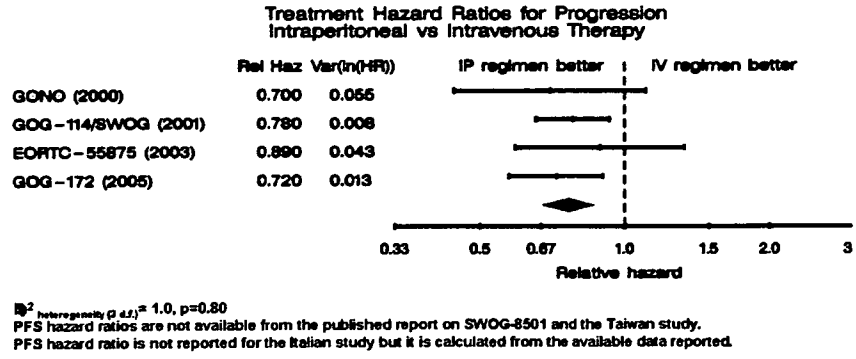

Figure 3. Hazard ratio of progression from meta-analysis, IP versus IV chemotherapy (adopted from NCI Clinical Alert).

At the same time when this important result was published, another important result of GOG 111 trial was published[59]. In this trial, it was shown that replacing cyclophosphamide with paclitaxel improved the median survival from 24 (95% CI 21–30) to 38 (95% CI 32–44) months (relative risk 0.6; 95% CI 0.5–0.8; $P < 0.001$) in advanced ovarian cancer. Therefore, the consensus at the time was that replacing cyclophosphamide with paclitaxel is more beneficial than applying IP administration of cisplatin.

A second IP trial was also conducted by GOG and SWOG, and the result was published in 2001[54]. In this trial, the patients were randomized to either IV paclitaxel 135 mg/m^2 over 24 h followed by IV cisplatin 75 mg/m^2 every 3 weeks for six cycles or IV carboplatin (AUC 9) every 28 days for two cycles, then IV paclitaxel 135 mg/m^2 over 24 h followed by IP cisplatin at 100 mg/m^2 every 3 weeks for six cycles (Fig. 7). Improved progression-free survival (median 28 versus 22 months; relative risk 0.78; log rank $P = 0.01$, one tail) (Fig. 8) and overall survival (median 63 versus 52 months; relative risk 0.81; $P = 0.05$, one tail) of 426 assessable patients were observed in favor of the IP group (Fig. 9). However, toxicities greater than or equal to grade 3, including neutropenia, thrombocytopenia, and gastrointestinal and metabolic toxicities, were significantly more frequent in the IP group. As a result, 18% of the patients received less than two courses of IP therapy. In spite of the significant survival improvement in this study, gynecological oncology community did not accept the IP chemotherapy to be the standard treatment for ovarian cancer because there was a possibility that addition of two cycles of carboplatin treatment may contribute to the improvement of survival, and toxicity was excessive in the IP arm.

The third trial was conducted by GOG, and the result was recently published in 2006[57]. In this study, 417 eligible patients with optimally debulked stage III ovarian cancer were randomized either to IV paclitaxel (135 mg/m^2/24 h) followed by IV cisplatin (75 mg/m^2) or to IV paclitaxel (135 mg/m^2/24 h) followed by IP cisplatin (100 mg/m^2), plus IP paclitaxel (60 mg/m^2) on day 8 (Fig. 10). Treatments were

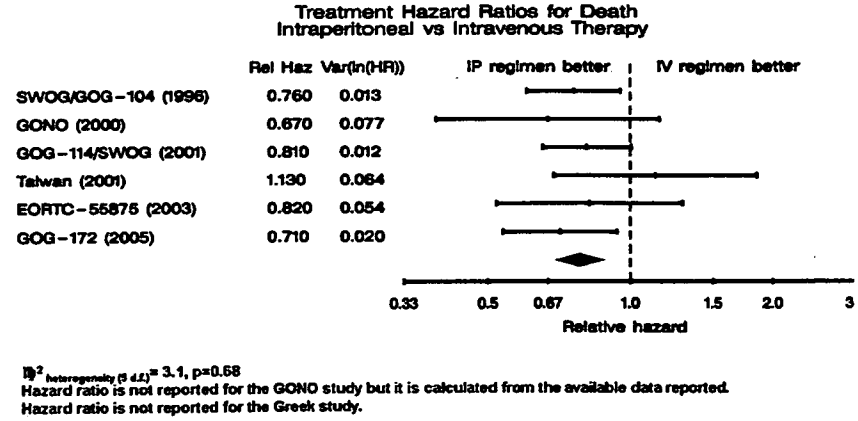

Figure 4. Hazard ratio of death from meta-analysis, IP versus IV chemotherapy (adopted from NCI Clinical Alert).

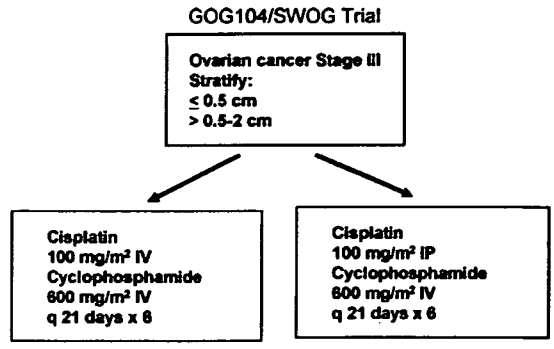

Figure 5. Trial design of GOG 104/SWOG study.

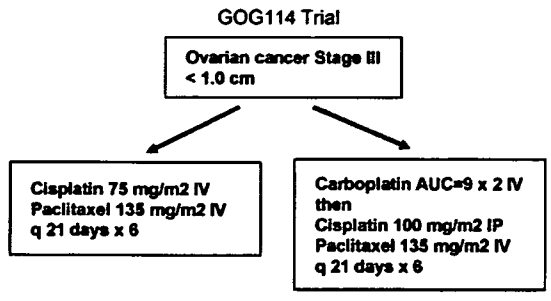

Figure 7. Trial design of GOG 114/SWOG study.

repeated every 21 days for six cycles. The relative risk of recurrence was 0.73 in the IP group versus IV group (Fig. 11). The improvement in median overall survival was 15.9 months, with a treatment hazard ratio of 0.75 (95% CI 0.58–0.97) favoring the IP study arm (Fig. 12). The magnitude of improvement in median overall survival associated with IP/IV administration of chemotherapy is similar to that observed with the introduction of either cisplatin or paclitaxel. The median duration of survival for IP arm of this trial (66 months) was 10 months longer than that for the current standard treatment schedule (IV paclitaxel plus IV carboplatin treatment) arm of GOG 158 trial (57 months). However, this survival advantage could be due to the addition of day 8 paclitaxel and not due to the IP delivery of cisplatin and paclitaxel. In addition, there were significantly more patients with grade 3/4 leukopenia, thrombocytopenia, and gastrointestinal toxicity, renal toxicity, neurologic toxicity, fatigue, infection, metabolic toxicity, and pain toxicity in the IP arm compared to the IV arm. Because of these toxicities and/or catheter problems, 48% of patients in the IP arm received three or fewer IP treatment, and only 42% patients received planned six cycles of IP therapy. As discussed by Cannistra[60], "it is remarkable that such a clinically meaningful survival advantage was observed, despite the high attrition rate in the intraperitoneal group, suggesting that a substantial benefit from intraperitoneal chemotherapy may occur within the first several cycles of treatment," and this trial posed the important questions to be solved in the future because it is hypothesized that improving catheter complications may enhance the survival benefit by IP chemotherapy further.

Some investigators, however, suggest that GOG 172 may overestimate the benefit of IP therapy. Ozols *et al.* have reported on a preliminary cross-trial analysis[61] comparing the results of IP therapy in GOG 172 with IV carboplatin/paclitaxel in 392 similarly staged patients (GOG 158)[62]. Instead of the 15.9-month improvement in median overall survival, the difference may be substantially less (8.2 months) if carboplatin/paclitaxel had been the comparative arm. There is no apparent difference in the actuarial survival curves and survival is very similar at 2 and 4 years. These investigators suggest that IP therapy

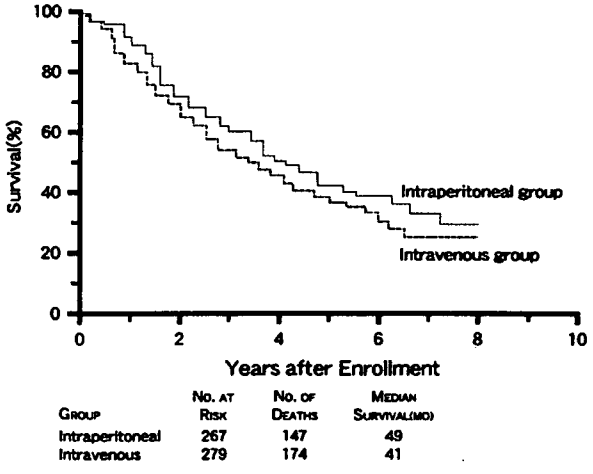

Figure 6. Overall survival of GOG 104/SWOG trial.

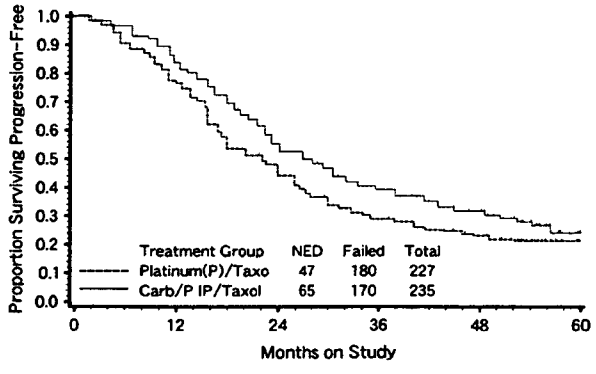

Figure 8. Progression-free survival of GOG 114/SWOG trial.

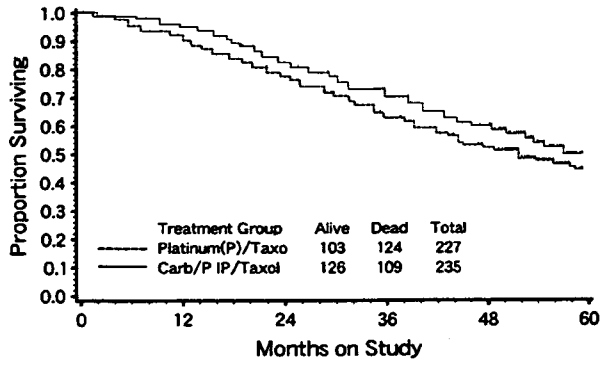

Figure 9. Overall survival of GOG 114/SWOG trial.

should be compared to a much less toxic regimen of IV carboplatin/paclitaxel, which in this exploratory cross-trial comparison appears to have very similar activity.

Toxicities and health-related quality of life

The comparison of toxicities in the phase III randomized trial between IV and IP chemotherapy is well summarized in the NCI Clinical Announcement for IP chemotherapy (Table 5). As shown in the table, various toxicities such as bone marrow suppressions, constitutional, gastrointestinal, neurologic symptoms, and infections were exceeded in the IP therapy arms in GOG 172 trial, although bone marrow and neurologic toxicities were less frequent in the GOG 104 trial. Bone marrow complications were also more frequent in the GOG 114 trial. The difference in the incident of these toxicities between trials was probably related to the addition of IV administration of AUC9 carboplatin in the GOG 114 trial and addition of IP paclitaxel in the GOG 172 trial. Abdominal pain was more frequent in patients on the IP arm of GOG 104 and GOG 172 trials.

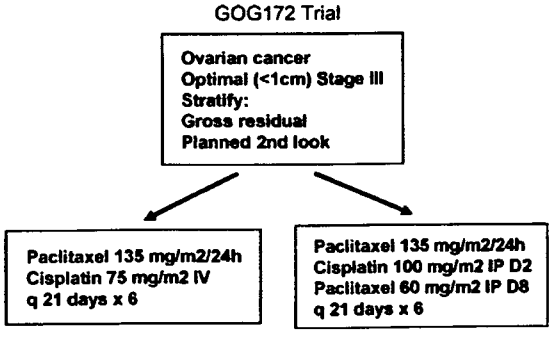

Figure 10. Trial design of GOG 172 study.

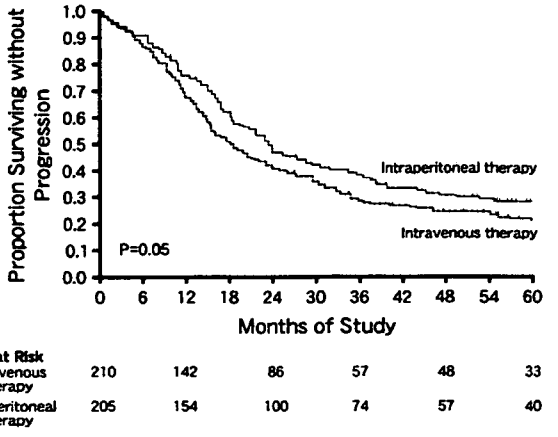

Figure 11. Progression-free survival of GOG 172 trial.

These toxicities may reduce the completion rate of planned cycles in IP treatment arm as summarized in Table 6. Completion rate of the planned treatment cycle in the GOG 172 arm is remarkably less than in IV arm (42% versus 90%). This may relate with the addition of IP administration of paclitaxel or other factors.

In the GOG 172 trial, health-related quality of life (HRQOL) particularly for the abdominal discomfort was assessed. Abdominal discomfort improved from baseline to chemotherapy cycle 4 for patients on both the IV and IP/IV chemotherapy arms. The improvement was greater in the IV arm. Better HRQOL among patients on the IV arm compared with patients on the combined IV/IP arm during and immediately after treatment was observed. However, these differences disappeared over time, so that at 1 year, HRQOL and pain scores were similar between the two groups except for paresthesias, which were more likely to

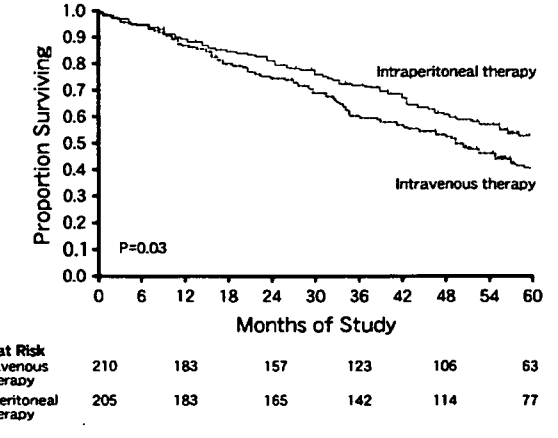

Figure 12. Overall survival of GOG 172 trial.