Phase II/III study of intraperitoneal chemotherapy after neoadjuvant chemotherapy for ovarian cancer: NCIC CTG OV.21

H.J. Mackay MBChB MD, D. Provencheur MD,† M. Heywood MD,‡ D. Tu PhD,§ E.A. Eisenhauer MD,§ A.M. Oza MB BS MD,* and R. Meyer MD§*

ABSTRACT

Three large randomized clinical trials have shown a survival benefit in women with stage III epithelial ovarian cancer (EOC) who receive intraperitoneal (IP) chemotherapy after optimal primary debulking surgery. The most recent Gynecologic Oncology Group study, GOG 172, showed an improvement in median overall survival of approximately 17 months. That result led to a U.S. National Cancer Institute (NCI) clinical announcement recommending that IP chemotherapy be considered for this group of women with EOC. However, IP chemotherapy is associated with increased toxicity, and rates for completion of treatment are low (42% in GOG 172). The optimal IP regimen and duration of treatment has yet to be defined. Women undergoing chemotherapy before optimal debulking surgery were not included in the studies or in the NCI clinical announcement. The National Cancer Institute of Canada Clinical Trials Group has developed a protocol for a randomized phase II/III study which will examine whether IP platinum–taxane-based chemotherapy benefits women who have received neoadjuvant chemotherapy before optimal surgical debulking. To address whether the less systemically toxic carboplatin can be substituted for cisplatin IP, the first phase of the study will have 3 arms: 1 intravenous-only, and 2 IP-containing regimens. At the end of the first stage, and provided that IP therapy is feasible to administer in this patient population, one of the IP regimens, either IP carboplatin or IP cisplatin, will proceed into a phase III comparison with the intravenous arm. This exciting new study has gathered international support.

KEY WORDS

Intraperitoneal chemotherapy, epithelial ovarian cancer, neoadjuvant chemotherapy, NCIC CTG OV.21

1. INTRODUCTION

Epithelial ovarian cancer (EOC) is the leading cause of gynecologic malignancy death in North America [1]. Despite the efficacy of intravenous (IV) platinum and paclitaxel chemotherapy, more than 75% of patients with stage III and IV EOC ultimately relapse and die of their disease [2].

1.1 INTRAPERITONEAL CHEMOTHERAPY

The peritoneal cavity is the principle site of spread and recurrence in women with EOC. Intraperitoneal (IP) administration of chemotherapy, as a means of increasing the dose intensity delivered to the tumour while minimizing systemic toxicity, is therefore an attractive therapeutic approach [3]. Advantages of this administration route include high IP concentration and longer half-life of the drug in the peritoneal cavity than are observed with IV administration. For cisplatin, the most commonly used IP chemotherapeutic agent, IP administration translates into an exposure in the peritoneal cavity that is greater by a factor of 10–20 than is achievable with the IV route [4]. Publication of the Gynecologic Oncology Group (GOG) 172 study, which demonstrated a significant overall survival benefit (17.4 months) for IP paclitaxel–IV cisplatin over conventional IV chemotherapy in women with stage III EOC undergoing "upfront" optimal (≤1 cm) debulking surgery prompted a re-evaluation of IP chemotherapy [5]. The U.S. National Cancer Institute (NCI) reviewed data from seven randomized trials comparing IV–IP with standard IV administration of chemotherapy in women who had undergone primary debulking surgery (Table I). On average, IP–IV chemotherapy was associated with a 21.6% decrease in risk of death (hazard ratio: 0.78; 95% confidence interval: 0.69 to 0.89) [5–12]. They concluded that IP–IV chemotherapy should be considered a standard of care for a select group of women with EOC.

Despite the favourable outcomes, IP chemotherapy has not been universally adopted. In all seven studies, toxicity was higher in the experimental arm, particularly when considered in comparison with standard IV carboplatin and paclitaxel. Drop-out rates were high, with completion rates ranging from 71% (GOG 114) to 42% (GOG 172). The optimal

TABLE I Summary of randomized clinical trials of intraperitoneal (IP) chemotherapy for "upfront" primary debulking surgery

Study and reference	*Regimens*		*Patients*	
	Control	*Experimental*	*Eligibility*	*(n)*
Kirmani *et al.,* 1994 [6]	Cisplatin 100 mg/m^2 IV, cyclophosphamide 600 mg/m^2, every 3 weeks for 6 cycles	Cisplatin 200 mg/m^2 IP, etoposide 350 mg/m^2 IP, every 4 weeks for 6 cycles	Stage IIC–IV	62
SWOG 8501/GOG 104 (Alberts *et al.,* 1996 [7])	Cisplatin 100 mg/m^2 IV, cyclophosphamide 600 mg/m^2 IV, every 3 weeks for 6 cycles	Cisplatin 100 mg/m^2 IP, cyclophosphamide 600 mg/m^2 IV, every 3 weeks for 6 cycles	Stage III, ≤2 cm residual	546
Polyzos *et al.,* 1999 [8]	Carboplatin 350 mg/m^2 IV, cyclophosphamide 600 mg/m^2 IV, every 3 weeks for 6 cycles	Carboplatin 350 mg/m^2 IP, cyclophosphamide 600 mg/m^2 IV, every 3 weeks for 6 cycles	Stage III	90
GONO (Gadducci *et al.,* 2000 [9])	Cisplatin 50 mg/m^2 IV, cyclophosphamide 600 mg/m^2 IV, epidoxorubicin 60 mg/m^2 IV, every 4 weeks for 6 cycles	Cisplatin 50 mg/m^2 IP, cyclophosphamide 600 mg/m^2 IV, epirubicin 60 mg/m^2 IV, every 4 weeks for 6 cycles	Stage II–IV, <2 cm residual	113
GOG 114/SWOG 9227 (Markman *et al.,* 2001 [10])	Cisplatin 75 mg/m^2 IV, paclitaxel 135 mg/m^2 24-h IV, every 3 weeks for 6 cycles	Carboplatin (AUC 9) IV every 28 days for 2 cycles, cisplatin 100 mg/m^2 IP, paclitaxel 135 mg/m^2 24-h IV, every 3 weeks for 6 cycles	Stage III, ≤1 cm residual	462
Yen *et al.,* 2001 [11]	Cisplatin 50 mg/m^2 IV, cyclophosphamide 50 mg/m^2 IV, epirubicin/doxorubicin 50 mg/m^2 IV, every 3 weeks for 6 cycles	Cisplatin 100 mg/m^2 IP, cyclophosphamide 500 mg/m^2 IV, epirubicin/doxorubicin 50 mg/m^2 IV, every 3 weeks for 6 cycles	Stage III, ≤1 cm residual	118
GOG 172 (Armstrong *et al.,* 2006 [5])	Cisplatin 75 mg/m^2 IV, paclitaxel 135 mg/m^2 24-h IV, every 3 weeks for 6 cycles	Paclitaxel 135 mg/m^2 24-h IV, cisplatin 100 mg/m^2 IP, paclitaxel 60 mg/m^2 IP on day 8, every 3 weeks for 6 cycles	Stage III, ≤1 cm residual	415

IV = intravenously; SWOG = Southwest Oncology Group; GOG = Gynecologic Oncology Group; GONO = Gruppo Oncologico Nord Ovest; AUC = area under the curve.

duration and regimen for IP–IV chemotherapy has therefore yet to be defined [12,13]. To date, the evidence for the IP–IV approach has been limited to women who undergo upfront optimal debulking surgery; those who undergo chemotherapy before a primary debulking surgical attempt are not included in the randomized studies.

1.2 "Neoadjuvant" Chemotherapy and Debulking Surgery

"Neoadjuvant chemotherapy" refers to the administration of chemotherapy before a definitive surgical debulking attempt. This approach was introduced into the management of ovarian cancer at the end of the 1980s [14], initially for women who were judged medically unfit to tolerate aggressive debulking surgery. Subsequently, neoadjuvant chemotherapy was advocated especially for the treatment of stage IV ovarian cancer, for patients with a very high metastatic tumour load, or for patients with poor general condition [15,16]. Furthermore, recent data (presented in abstract form) from the European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group (EORTC GCG) in cooperation with the NCIC Clinical Trials Group (CTG) (EORTC 55971/CTG OV.13) suggest that, in stage IIIC–IV ovarian cancer, neoadjuvant chemotherapy followed by debulking surgery produces overall survival and progression-free survival (PFS) outcomes that are similar to, but with less toxicity than, those seen with standard primary debulking surgery followed by chemotherapy [17]. Thus, interest in neoadjuvant chemotherapy has increased, and its use has become widespread in many centers [18].

Debulking surgery is usually attempted after 3 or 4 cycles of chemotherapy, which is the preferred duration of neoadjuvant therapy for several reasons:

- Chemotherapy-induced fibrosis is less extensive after 3 cycles than after 6 cycles, thus easing surgical resection [19].
- Patients who continue to have bulky disease after 6 cycles of chemotherapy are more likely to have

chemoresistant disease, and their ultimate prognosis may not warrant an attempt at aggressive surgical resection [20].
- Extensive courses of chemotherapy before surgery may compromise the ability to deliver chemotherapy postoperatively.

We postulate that patients undergoing optimal (≤1 cm) debulking after neoadjuvant chemotherapy may derive a survival benefit from IP–IV chemotherapy that is similar to the benefit seen in women who undergo IP–IV chemotherapy after optimal upfront debulking surgery.

2. NCIC CTG OV.21

The two-stage randomized OV.21 trial will compare IV chemotherapy with platinum-based IP–IV chemotherapy in women who have undergone optimal (≤1 cm residual disease) surgical debulking after 3 or 4 cycles of neoadjuvant platinum-based IV chemotherapy (Figure 1). Women will be enrolled either postoperatively after the debulking surgery has been performed, or if they have previously given consent, intraoperatively, thus giving the surgeon the option to place the IP catheter at the time of surgery if the patient is randomized to an IP study arm. Although the study is led by the NCIC CTG, the protocol, the accompanying IP therapy guidelines, and a companion document intended to summarize and promote best practice in the administration of IP therapy are the result of a collaboration between the NCIC CTG and the Society of Gynecologic Oncologists of Canada, with international partners in the United Kingdom (National Cancer Research Institute), Spain (Spanish Ovarian Cancer Research Group), and the United States (Southwest Oncology Group).

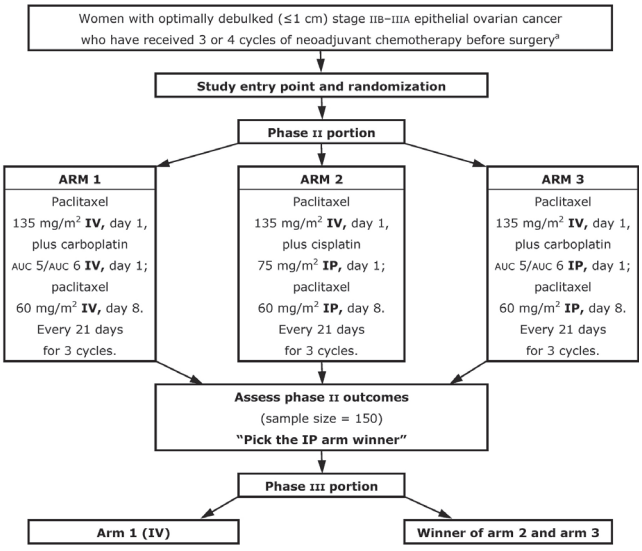

FIGURE 1 Study schema. [a] Patients with stage IV disease by virtue of the presence of pleural effusion will are also be eligible. IV = intravenously; AUC = area under the curve; IP = intraperitoneally.

2.1 Study Design

2.1.1 Phase II

The study will initially consist of a 3-arm randomized phase II trial (Figure 1) with 2 IP–IV arms (based on IP cisplatin and carboplatin respectively) and an IV arm. At this stage of the study, 150 patients will be enrolled (50 to each arm), with the primary aim being to "pick the winner" between the two IP arms, provided that it is feasible and safe to deliver IP chemotherapy to the study population. The study will then proceed with an expanded 2-arm phase III study in which the chosen IP arm will be compared with the IV arm. The "pick the winner" decision between the IP carboplatin and IP cisplatin arms will be based on the progressive disease (PD) rate at 9 months (as a surrogate measure of efficacy) and on toxicity. For the two IP arms, the null hypothesis that the true PD rate at 9 months is 52.5% or higher (by one-sided test at the 0.05 level) will first be tested; the "winning" arm will then be picked up for phase III study by a comparison of the observed 9-month PD rates. Should neither IP arm reach the required level, the study will be closed at the first stage of accrual. Data will be reviewed by an independent data safety monitoring committee, and a recommendation will be made to the trial management committee about both continuation of the study and choice of the IP (experimental) arm. Patients will be recruited to the IV arm as well as to the 2 IP arms during the phase II portion of the study; this approach is intended to reduce the risk of selection bias in the interpretation of outcomes for patients allocated to IP therapy.

2.1.2 Phase III

The primary objective of the phase III portion of the study is to compare the efficacy of 3 cycles of the selected IP–IV chemotherapy regimen with IV carboplatin plus paclitaxel in patients with optimally surgically debulked EOC after neoadjuvant IV chemotherapy. The primary endpoint for assessment of efficacy will be PFS. Secondary objectives include overall survival, toxic effects, quality of life, economic evaluation, and correlative biology studies. A novel nursing study will investigate aspects of nursing practice associated with administration of IP therapy. A further 630 patients will be recruited into this phase of the study. The trial is projected to take approximately 4.5 years to complete accrual.

2.2 Rationale for the Study Arms

The basis of the experimental arms in all the randomized IP clinical trials has been IP cisplatin [5–12]. However, that agent, delivered by that route, is associated with significant toxicity, particularly neuropathy and

emesis. In the 10 years between the initial IP studies and the NCI announcement, IV carboplatin replaced IV cisplatin as the agent of choice for standard IV chemotherapy delivered to patients with EOC. However, questions remain about whether IP delivery of carboplatin is (as we suspect) safer than and as efficacious as IP delivery of cisplatin.

Although proceeding to a randomized phase III study was potentially desirable, the feeling was that, in the absence of randomized trial data, it was inappropriate to use an IP carboplatin–based regimen in what is a new patient population without some form of evaluation comparing it with both IV chemotherapy and an IP cisplatin–based regimen. Hence, 2 IP regimens were included in the initial stage of the study.

In line with earlier studies, IV paclitaxel is included in both IP arms. The 24-hour schedule used in GOG 172 will be replaced by the more convenient, and equally efficacious, 3-hour infusion of paclitaxel [5,21]. Data suggest that same-day administration with IP cisplatin is safe and does not result in an increased rate of neurotoxicity [22]. Given the data from GOG 172, day 8 IP paclitaxel will be included in both experimental arms [5].

All three of the large randomized trials administered IP cisplatin at a dose of 100 mg/m^2 every 3 weeks [5,7,10,12]. That dose forms the basis of the NCI recommendation. However, at that dose, cisplatin-related toxicity was considerable and completion rates were low. Studies using IV cisplatin have demonstrated a steep dose–response effect for serious drug-related toxicity, particularly emesis [23]. Many practitioners therefore reduce the dose of IP cisplatin to improve tolerability. Given the high IP concentrations of the drug, a modest reduction in systemic exposure resulting from reducing the IP dose to 75 mg/m^2 was felt to be unlikely to affect efficacy. Hence, 75 mg/m^2 has been selected for the OV.21 study.

The control arm for the study consists of IV carboplatin and paclitaxel administered for 3 cycles. At the 2008 meeting of the American Society of Clinical Oncology, the Japanese Gynecologic Oncology Group (JGOG) presented the mature PFS data from their randomized trial of standard every-3-weeks IV carboplatin compared with either weekly or every-3-weeks paclitaxel [24]. They observed a significant prolongation of PFS (to 28 months from 17 months) in the weekly arm. Because the most recent IP study [5] used days 1 and 8 paclitaxel dosing, it has been postulated that, given the JGOG data, some of the observed benefit may be related to the day 8 dose of paclitaxel and not to the IP route of administration. In OV.21, we will avoid this confounder by keeping the dose and schedule of paclitaxel the same in all arms. Data suggest that the dose and schedule selected for the control arm of our study should not place patients at increased risk of additional treatment-related toxicity [24–26].

2.3 Study Population

The study population will consist of women who have a histologically confirmed diagnosis of advanced EOC or of primary (serous) peritoneal or fallopian tube cancer, and who have undergone optimal (≤1 cm) delayed primary debulking surgery after 3 or 4 cycles of neoadjuvant platinum-based chemotherapy. The main eligibility criteria are these:

- Stage IIB–III disease at initial diagnosis, based on clinical and imaging assessment (patients with stage IV disease by virtue of the presence of one or more pleural effusions will also be eligible)
- Surgery occurring no more than 4 weeks after completion of neoadjuvant chemotherapy (total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and any additional surgical procedure required to achieve maximal cytoreduction with residual disease of 1 cm or less as assessed by the surgeon at the end of surgery)
- Study therapy start within 6 weeks of surgery
- Performance status (Eastern Cooperative Oncology Group) of 2 or lower and adequate organ function

Patients who have unresolved toxicity or who experienced an allergic reaction to preoperative chemotherapy will not be eligible. Because IP chemotherapy requires a substantial fluid load, patients who have a significant cardiac history or any other medical condition that might make them unsuitable for IP therapy will be excluded. Given that the success of the IP approach requires the chemotherapeutic agent to come into contact with residual tumour, patients with extensive adhesions or any other feature that might hinder free movement of fluid within the peritoneal cavity (as determined by the surgeon) will also be excluded.

To ensure patient safety, patients who consent to the study preoperatively and who undergo intraoperative randomization will have to meet all the foregoing criteria at the time of randomization and will have to be assessed within 7 days of study therapy start to ensure that they meet patient safety criteria.

2.4 Secondary Aims (Phase III Only)

2.4.1 Health-Related Quality of Life

Health-related quality of life (QOL) is relevant to cancer patients because it measures, from the patient perspective, the symptom-related and functional benefits associated with the balance between control of the underlying cancer and detrimental effects associated with the cancer experience, including receiving anticancer therapy [27]. It is hypothesized that IP treatment may be associated with specific adverse effects, including abdominal symptoms that may be in excess of those experienced by patients receiving IV therapy. Thus, assessment of QOL may provide information

complementary to the assessment of PFS. Furthermore, should IP therapy be shown to lead to an improvement in survival, QOL results may further inform health care providers and patients of any potential trade-offs associated with the choice of treatment options. During the second stage of recruitment, patient QOL will be assessed using a validated instrument—the EORTC C30 Quality of Life Questionnaire (QLQ) [28,29], with ovarian cancer module EORTC QLQ OV28 [30,31]—and to measure neurotoxicity, the Functional Assessment of Cancer Therapy/GOG-Neurotoxicity subscale [32].

2.4.2 Health Economics

Health economics is important to cancer patients, health care providers, policymakers, and society, because it evaluates the value of an intervention. Value is determined by examining the costs associated with the intervention and its management and considers the benefits (including prolongation of survival and QOL) of the intervention and its management. Determining economic value is of particular relevance in OV.21, because IP therapy is associated with consumption of additional hospital-based resources. The economic analyses will compare, for the randomized groups, the incremental costs associated with the competing options, including analyses of both cost-effectiveness and cost–utility, thus taking into account the perspectives both of society and of provincial ministries of health.

2.4.3 Correlative Studies

Understandings of the biologic mechanisms and markers of ovarian cancer and of their relations to therapy can be facilitated by linking evaluations of those parameters with the outcomes of patients receiving various treatments by random allocation. The OV.21 trial provides an opportunity to evaluate potential prognostic biologic markers and markers predictive of superior outcome with one of the competing treatment alternatives being tested. The trial does not include a prospectively-determined embedded correlative question. However, acquisition of tumour specimens both before study therapy is started and after neoadjuvant chemotherapy has been received provides a unique opportunity for a correlative study of differing drug responses within the same patients.

2.4.4 Evaluation of Outcomes Related to Nursing Management

An exciting part of the OV.21 study is that, for the first time, it provides an opportunity to prospectively answer some basic questions relating to best nursing practice and the delivery of IP chemotherapy. The phase III portion of the trial will therefore include a survey of nursing practices associated with administration of IP chemotherapy. The goal of these assessments will be to facilitate an understanding of various nursing practices related to patient positioning during and after administration of IP therapy; the pre-warming of IP fluids; and use of home hydration practices and how they affect patient outcome and QOL.

5. SUMMARY

On average, IP chemotherapy was associated with a 21.6% decrease in risk of death, translating into a 12-month increase in median overall survival for women with optimally debulked (≤1 cm) stage III EOC.

The NCIC CTG OV.21 study represents an exciting opportunity to try to improve the outlook for the increasing number of women undergoing neoadjuvant chemotherapy before optimal debulking surgery for advanced EOC. The pragmatic design allows for some flexibility both in the chemotherapy regimen (provided that it is platinum-based) and the number of cycles (3 or 4) delivered in the neoadjuvant setting before study enrolment. By randomizing patients to receive either 3 cycles of IP or 3 cycles of IV chemotherapy, it will be possible to determine whether, in this group of women, IP chemotherapy conveys a survival benefit that is similar to the benefit seen in women undergoing surgery before chemotherapy. Furthermore, its innovative design allows for an evaluation of a less-toxic alternative to standard IP cisplatin chemotherapy; thus, data from this study may have broader implications for all women receiving IP chemotherapy for EOC.

6. CONFLICT OF INTEREST DISCLOSURES

The NCIC is the funder of OV.21. The authors have no financial conflicts of interest to declare.

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Correspondence to: Helen J. Mackay, Division of Medical Oncology and Hematology, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario M5G 2M9.
E-mail: Helen.Mackay@uhn.on.ca

* Princess Margaret Hospital, Toronto, ON.
† Gynécologie Oncologique, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montreal, QC.
‡ BC Cancer Agency, Vancouver, BC.
§ National Cancer Institute of Canada, Clinical Trials Group, Kingston, ON.