

THE USE OF INTRAPERITONEAL CHEMOTHERAPY FOR OVARIAN CANCER

In January 2006 the National Cancer Institute (NCI) USA published a clinical announcement to clarify the role of intraperitoneal chemotherapy for ovarian cancer, based on a systematic review of randomised controlled trials.

A summary of the findings developed by the National Breast Cancer Centre is provided below. The conclusions of this summary are based on evidence available to Oct 2006. New data are constantly emerging. The conclusions of this summary are likely to change with longer follow-up periods and in light of evidence from other trials.

To access the full NCI review click on the following link:

<http://www.gog.org/ipchemoed/clinicalann.pdf>

WHAT IS INTRAPERITONEAL CHEMOTHERAPY?

Intraperitoneal (IP) chemotherapy is treatment in which anticancer drugs are given through a surgically implanted catheter into the woman's peritoneal cavity (abdomen), the most common site of spread or recurrence. The aim of IP chemotherapy for ovarian cancer is to remove cancer remaining in the abdomen following primary cytoreductive surgery.

CURRENT USE OF INTRAPERITONEAL CHEMOTHERAPY

IP chemotherapy is currently not recognised as standard treatment for women with ovarian cancer, however its use may be considered on an individual case by case basis. The optimal drug and dose for IP therapy have not been determined.

SYSTEMATIC REVIEW OF EVIDENCE

The National Cancer Institute (NCI) undertook a systematic review that focused on seven randomised trials comparing intravenous (IV) versus IP or IP/IV treatment for first-line treatment of ovarian cancer, conducted between 1994 and 2006. (A list of the summarised trial characteristics is provided in Table 1).

In all trials chemotherapy was given after primary surgery. The women recruited for the trials were all classified as having advanced ovarian cancer (stage IIC - stage IV). Residual disease status was variously designated, with a range between less than or equal to 1 cm to less than or equal to 2 cm. Although each study used different regimens of chemotherapy drugs all studies used either cisplatin or carboplatin IP. Additionally, a range of non-platinum drugs were used across the studies including cyclophosphamide, anthracyclines, etoposide and paclitaxel.

RESULTS

EFFICACY

Seven randomised phase III trials assessing IP chemotherapy for the first-line treatment of ovarian cancer were reviewed. IP chemotherapy was associated, on average, with a 21.6% decrease in the risk of death (Hazard Ratio (HR) 0.79, 95% confidence interval (CI) 0.70-0.89).

The most recent trial conducted by the Gynecologic Oncology Group¹ showed survival benefits of combined IP/IV chemotherapy over IV chemotherapy alone. This study involved 429 women with stage III ovarian cancer who were given chemotherapy following surgery. IV cisplatin and IV paclitaxel were compared with IV paclitaxel and IP paclitaxel plus IP cisplatin. Women receiving IP chemotherapy had significantly improved overall survival. The improvement in median overall survival with IP/IV administration was 15.9 months with a treatment HR 0.75 (95% CI 0.58 – 0.97).

Due to toxic side effects, only 42% of patients completed six cycles of the planned IP chemotherapy. The most common reason for discontinuation of IP therapy was catheter complications.

Two early studies by Alberts *et al*³ and Markman *et al*⁴ also found that median survival was significantly longer for patients receiving IV/IP chemotherapy compared with IV chemotherapy. Both these studies were conducted in patients with stage III ovarian cancer with minimal residual disease. Three other studies^{5, 6, 7} compared IP chemotherapy with IV chemotherapy, however these studies did not reveal a significant survival benefit of either therapy. (Median survival time for randomised trials comparing IV versus IV/IP first line treatment for ovarian cancer are summarised in Table 2.)

In a number of the trials^{1, 3, 4} the optimal number of IP treatments was limited due to side effects. Despite patients being unable to complete their full treatment, studies still demonstrated a survival benefit. It remains unclear what the optimal regimen of IP treatments is for women with ovarian cancer.

TOXICITY

Side effects of IP chemotherapy were associated with the type of chemotherapy used, administration of the IP chemotherapy and catheter-related complications. Overall, the results of the studies found that the risk of infection was higher among patients receiving IP compared to IV chemotherapy. Patients receiving IP chemotherapy were more likely to experience abdominal pain or discomfort, increased fever, nausea and vomiting. Other IP

issues related to catheter use included intra-abdominal infection, prolonged ileus, bowel obstruction and bowel perforation.

Patients receiving IP cisplatin experienced side effects such as tinnitus, neutropenia and hearing loss, while patients receiving IP paclitaxel experienced more abdominal pain. A recent study by Fujiwara *et al*² suggests that chemotherapy-related side effects could be reduced by replacing IP cisplatin with IP carboplatin.

QUALITY OF LIFE

Side effects related to IP chemotherapy were usually short-term and manageable. The most recent study¹ found that although women who received IP chemotherapy had more side effects during treatment, their reported quality of life a year after treatment was similar to women treated with IV chemotherapy alone. The optimal management of side effects associated with IP chemotherapy has yet to be established.

WHICH PATIENTS MAY BENEFIT FROM IP CHEMOTHERAPY?

Based on the findings from GOG172, the patients who may benefit from IP chemotherapy are women with advanced (FIGO stage III) ovarian cancer who have undergone optimal cytoreductive surgery to no or minimal residual tumour. In patients where IP chemotherapy is an option, this should be discussed prior to surgery taking place to ensure women have a clear understanding of both the potential benefits and side effects of the treatment.

WHICH PATIENTS MAY NOT BENEFIT FROM IP CHEMOTHERAPY?

There are no data to indicate whether IP chemotherapy will benefit in women:

- with stage IV ovarian cancer who have undergone optimal cytoreductive surgery
- with stage III ovarian cancer who have residual tumor greater than one centimetre in diameter after cytoreductive surgery
- who undergo interval cytoreductive surgery after neoadjuvant chemotherapy or initial suboptimal cytoreductive surgery followed by several courses of IV chemotherapy and are then left with no or minimal residual disease
- with no or minimal residual disease after surgery and standard platinum-and-taxane IV chemotherapy
- with early stage (stage I or II) ovarian cancer
- with recurrent ovarian cancer
- with extensive intra-abdominal adhesions
- with significant surgical complications or post-operative infectious complications.

RESPONSE TO THE GOG172 RESULTS AND NCI CLINICAL ANNOUNCEMENT

Since the publication of the results of the GOG172 trial and the NCI clinical announcement, a number of papers have been published reviewing the data and recommendations about IP chemotherapy.

The German Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) and the two German cooperative study groups (AGO-OVAR and NOGGO) concluded that while the data presented from GOG172 contributed to the discussion about IP chemotherapy, the trial does not justify a change of standard. It was acknowledged that IP chemotherapy has shown some survival benefit in the three large, randomised trials and might be a sensible alternative for a subgroup of patients with advanced ovarian cancer. While the regimen used in the GOG172 trial was not considered to be tolerable, the study groups noted that other unevaluated IP regimens such as carboplatin-paclitaxel should not uncritically administered. *The paper concluded that IP chemotherapy was not considered to be appropriate for administration outside the clinical trial setting and that the existing guidelines about the treatment of advanced ovarian cancer, using IV administration of carboplatin-paclitaxel, are still valid.*⁸

A group, from the University of Ottawa in Canada, assessed the position of Canadian gynaecological oncologists (GOC) towards IP chemotherapy as primary treatment for ovarian cancer and the barriers to implementing IP across Canada, using an electronic survey. At the time of the survey most GOCs were not offering IP to women who had undergone optimal debulking surgery, so IP chemotherapy will represent a relatively new modality of treatment in most Canadian centres. Most GOCs were developing an IP chemotherapy protocol and but had not yet finalised the chemotherapy regimen. *More than half the respondents were concerned about the management of systemic and local toxicities, catheter complications, and patients' quality of life and acceptance of treatment. Concerns were also raised around the cost of implementing IP chemotherapy and impact on hospital resources. The GOCs also noted the toxicity associated with the use of cisplatin in the trials, and the lack of phase III setting testing of carboplatin, which has replaced cisplatin as standard IV therapy.*⁹

In a paper published in the *Journal of Clinical Oncology*,¹⁰ medical oncologists from the Royal Marsden Hospital in the UK, the Dr Horst-Schmidt-Klink in Germany and the Katholieke Universiteit Leuven in Belgium. reviewed the data from GOG172 and noted a number of areas of concern, including poor trial design, the fact that the analysis was not truly based on 'intention to treat' and the loss to follow up. *The authors do not support the use of IP chemotherapy as a standard of care and concluded that at the present time there is no IP regimen to offer women that is both safe and has Level 1 evidence for efficacy compared to the standard care - IV carboplatin and paclitaxel.*

In a paper published in the *Annals of Oncology*,¹¹ Vermoken noted that while the design of the most recent US trial of IP (GOG172) was more complicated, the survival data

indicates that IV/IP treatment, whatever the reason and despite the fact that it is more difficult and a more complicated treatment than IV therapy, seems to lead to a better survival in patients with optimally debulked stage III ovarian cancer. *It is noted that the presently advised regimen is not the final answer, considering the toxicities observed, and that the indications for IP chemotherapy should not go beyond that for which adequate information is available. The need for adequate training, skill and experience in the administration of IP chemotherapy are acknowledged, with issues still to be resolved around the toxicity profile, catheter usage, timing and the appropriate number of cycles.*

OUTSTANDING ISSUES FOR THE AUSTRALIAN CONTEXT

The recommendation in the Australian Clinical practice guidelines for the management of women with epithelial ovarian cancer (2004) developed by the National Breast Cancer Centre and the Australian Cancer Network states that while intraperitoneal chemotherapy is currently not recognised as standard treatment for women with ovarian cancer, its use may be considered on an individual patient basis at a designated cancer centre with experience in this type of treatment.

The introduction of IP chemotherapy will require the development of health service standards and guidelines for practice. The National Breast Cancer Centre will work with experts to develop service level standards of care for facilities providing IP chemotherapy in Australia.

The Australian New Zealand Gynaecological Oncology Group (ANZGOG) will undertake a phase II trial of IP chemotherapy for primary ovarian peritoneal cancer (TRIPOD) in 2006. Women in this study will receive six cycles of cisplatin and paclitaxel IP, with the additional paclitaxel given intravenously. The trial will determine the regimen's feasibility, tolerability, and effects on quality of life.

CONCLUSIONS

IP chemotherapy is more complex than IV chemotherapy. IP chemotherapy requires specialist knowledge and experience to perform effective cytoreductive surgery, in the placement of the catheter and the administration of the chemotherapy. Current research shows that compared with IV administration alone, a combination of IV and IP administration of chemotherapy provides a significant survival benefit among women with stage III ovarian cancer. However, issues associated with the administration of IP and the management of complications needs further investigation. Further trials need to be conducted to determine optimal number of IP treatments and dosage which are still effective but have fewer side effects.

Table 1. Randomized trials comparing IV versus IP or IP/IV first-line treatment of ovarian cancer

Study identifier/ year published	Control regimen	Experimental regimen	Eligible patients	Number of patients
Kirmani et al., 1994	Cisplatin 100 mg/m ² IV; Cyclophosphamide 600 mg/m ² Q 3 weeks x 6	Cisplatin 200 mg/m ² IP; etoposide 350 mg/m ² IP Q 4 weeks x 6	Stage IIC-IV	62
SWOG 8501/ GOG 104 Alberts et al., 1996	Cisplatin 100 mg/m ² IV; Cyclophosphamide 600 mg/m ² IV Q 3 weeks x 6	Cisplatin 100 mg/m ² IP; Cyclophosphamide 600 mg/m ² IV Q 3 weeks x 6	Stage III, ≤ 2 cm residual	546
Polyzos et al., 1999	Carboplatin 350 mg/m ² IV; Cyclophosphamide 600 mg/m ² IV Q 3 weeks x 6	Carboplatin 350 mg/m ² IP; Cyclophosphamide 600 mg/m ² IV Q 3 weeks x 6	Stage III	90
Gadducci et al., 2000	Cisplatin 50 mg/m ² IV; Cyclophosphamide 600 mg/m ² IV; Epidoxorubicin 60 mg/m ² IV Q 4 weeks x 6	Cisplatin 50 mg/m ² IP; Cyclophosphamide 600 mg/m ² IV; Epidoxirubicin 60 mg/m ² IV Q 4 weeks x 6	Stage II-IV, < 2 cm residual	113
GOG 114/ SWOG 9227 Markman et al., 2001	Cisplatin 75 mg/m ² IV Paclitaxel 135 mg/m ² (24 hr) IV Q 3 weeks x 6	Carboplatin (AUC9) IV q 28 days x 2; Cisplatin 100 mg/m ² IP; Paclitaxel 135 mg/m ² (24 hr) IV q 3 weeks x 6	Stage III, ≤ 1 cm residual	462
Yen et al., 2001	Cisplatin 50 mg/m ² IV; Cyclophosphamide 50 mg/m ² IV; Epidoroxorubin/ Doxorubicin 50 mg/m ² IV Q 3 weeks x 6	Cisplatin 100 mg/m ² IP Cyclophosphamide 500 mg/m ² IV; Epidoxirubicin/ Doxorubicin 50 mg/m ² IV Q 3 weeks x 6	Stage III, ≤ 1 cm residual	118
GOG 172 Armstrong et al., 2006	Cisplatin 75 mg/m ² IV; paclitaxel 135 mg/m ² (24 hr) IV Q 3 weeks x 6	Paclitaxel 135 mg/m ² (24 hr) IV; Cisplatin 100 mg/m ² IP; Paclitaxel 60 mg/m ² IP on day 8 Q 3 weeks x 6	Stage III, ≤ 1 cm residual	415

Notes: SWOG 8501/GOG 104 was conducted under the auspices of the NCI/Bristol Myers Squibb (BMS) cisplatin cooperation program. GOG 114/SWOG 9227 and GOG 172 were conducted under the auspices of the NCI/BMS Cooperative Research and Development Agreement for paclitaxel.

Table 2. Median survival time for randomized trials comparing IV versus IV/IP first-line treatment for ovarian cancer

Study identifier/authors/ year published	Number of patients	Median duration of survival for control regimen (months)	Median duration of survival for experimental regimen (months)
SWOG 8502/GOG 104, Alberts et al., 1996	546	41	49
Polyzos et al., 1999	90	52	63
Gadduci et al., 2000	113	25	26
GOG 114/SWOG 9227/ ECOG GO114 Markman et al, 2001	462	51	67
Yen et al., 2001	118	48	43
Armstrong et al., 2006	415	50	66

REFERENCES

1. Fujiwara K, Markman M, Morgan M et al. Intraperitoneal carboplatin-based chemotherapy for epithelial ovarian cancer. *Gynecol Oncol* 2005; 97:10-5.
2. Armstrong D, Bundy B, Wenzel L et al. Phase III randomized trial of intravenous cisplatin and paclitaxel versus an intensive regimen of intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel in stage III ovarian cancer: a Gynecologic Oncology Group study. *N Engl J Med* 2006; 354:34-43
3. Alberts DS, Markman M, Armstrong D et al. Intraperitoneal therapy for stage III ovarian cancer: a therapy whose times has come! *J Clin Oncol* 2002;20:3944-6
4. Markman M, Bundy BN, Wenzel L et al. Phase III randomized trial of intravenous cisplatin and paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001; 19; 1001-1007
5. Polyzos A, Tasvaris N, Kosmas C et al. A comparative study of intraperitoneal carboplatin versus intravenous carboplatin with intravenous cyclophosphamide in both arms as initial chemotherapy for stage III ovarian cancer. *Oncology* 1999;56:291-6
6. Yen M-S, Juang C-M, Lai C-R et al. Intraperitoneal cisplatin-based chemotherapy vs. intravenous cisplatin-based chemotherapy for stage III optimally cytoreduced epithelial ovarian cancer. *Int J Gynecol Obstet* 2001; 72:55-60
7. Gadducci A, Carnini F, Chiara S et al. Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologica Nord-Ovest. *Gynecol Oncol* 2000; 76:157-62
8. Du Bois A, Schmalfeldt B, Meier Q, Selhoul and Pfisterer J for the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Kommission Ovar, The AGO Study Group Ovarian Cancer (AGO-OVAR), and the Norddeutsche Gesellschaft Fuer Gynaekologische Onkologie (NOGGO). Ovarian cancer - can intraperitoneal therapy be regarded as the new standard in Germany? *Int J Gynecol Cancer* 2006; 16:1756-1760.
9. Alhayki M, Hopkins T. Le and Fung Kee Fung M. Intraperitoneal chemotherapy for advanced epithelial ovarian cancer: a Canadian perspective. *Int J Gynecol Cancer* 2006; 16: 1761-1765.
10. Gore M, du Bois A and Vergote I. Intraperitoneal chemotherapy in ovarian cancer remains experimental. *Journal of Clinical Oncology* 2006; 24: 4528-4530.
11. Vermorken J. Intraperitoneal chemotherapy in advanced ovarian cancer: recognition at last. *Annals of Oncology* 2006; 17 (Supplement 10): 241-246.