Selected Summary

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

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SUMMARY

Epithelial ovarian cancer (EOC) is a common gynaecological malignancy. About two third patients have advanced disease (FIGO stage III-IV) at diagnosis.[1] Initial debulking surgery followed by paclitaxel and platinum based chemotherapy is currently standard treatment approach.[2] Recurrence of disease in abdomen (intraperitoneal) is the main cause of treatment failure[1]. Earlier studies have suggested that intraperitoneal chemotherapy may help in reducing the risk of relapse of EOC.[3, 4] Present randomized study was conducted by the Gynecologic Oncology Group (GOG) to evaluate the role of intraperitoneal chemotherapy in advanced ovarian cancers.[5]

Between March 1998 and Jan 2001, 429 patients of stage III ovarian cancer and primary peritoneal cancers with residual disease <1cm after surgery were enrolled in the study. Patients were randomized to *intravenous group* (n=215) in which patients received intravenous paclitaxel 135mg/m^2 over a 24 hour period on day1 and intravenous cisplatin 75mg/m^2 on day 2 and *intraperitoneal group* (n=214) in which they received intravenous paclitaxel 135mg/m^2 over 24 hours on day 1, intraperitoneal cisplatin 100mg/m^2 on day 2 and intraperitoneal paclitaxel 60mg/m^2 on day 8. Eligibility criteria included - stage III epithelial ovarian or peritoneal carcinoma with residual disease =1 cm in diameter after surgery, GOG performance status 0-2, normal blood counts, and adequate renal and hepatic function. Intraperitoneal route was accessed by either using Tenckhoff catheters or port attached to venous catheters placed in a subcutaneous pocket overlying the inferior costal margin. Catheters were placed either during debulking surgery or delayed until randomization and inserted using mini laparotomy or laparoscopy few centimeters lateral to the umbilicus.[6] Informed written consent was taken from all the patients. Patients underwent physical examination, complete blood count, blood chemical levels and CA125 at baseline and before each cycle. This was repeated at completion of therapy, every 3 months for 2 years and then onwards every 6 monthly. Quality of life was assessed using Functional Assessment of Cancer Therapy-Ovarian (FACT-O) scores at registration, before cycle 4, after 6th cycle and 1 year of completion of therapy. Treatment was delayed in case of grade 3 or 4 peripheral neuropathy, creatinine >2mg/dl or creatinine clearance <50ml/min. The dose reduction of intraperitoneal drug was done if there was grade2 abdominal pain.

The dose of cisplatin was reduced if there was grade 2 peripheral neuropathy. Patients with intraperitoneal catheter related complications, grade 3 abdominal pain, recurrent grade 2 abdominal pain which was not relieved after dose reduction were excluded from intraperitoneal arm and received intravenous chemotherapy for rest of the cycles. Similarly, patients with treatment delay of 3 weeks were excluded from the study. Fourteen patients (intra - peritoneal group-9, intravenous group-5) were excluded from the study either due to nonepithelial histology (n=5), stage other than stage III (n=3), second primary cancer (n=1), different primary (n=1), inadequate surgery (n=2) and tumour with low malignant potential (n=2). Chemotherapy was given every 3 weeks to a total

of 6 cycles. Second look laparotomy, which was optional, was done within 8 weeks of completion of 6 cycles of chemotherapy. 141 patients underwent second look laparotomy.

Statistical analysis of survival was done using Kaplan-Meier method. The relative risk and confidence intervals for treatment effects were calculated using Cox model. Quality-of-life assessments from baseline to follow-up were analyzed with linear models with an unstructured covariance matrix.

83% (174 out of 210) patients completed total 6 cycles of chemotherapy in *intravenous group* whereas only 42% (86 out of 205) completed assigned total 6 cycles in *intraperitoneal group*. The rate of complete pathological response was high in *intraperitoneal group* (57% vs 41%,p=ns). All the therapy related toxicities were more in *intraperitoneal group*. Statistically significant (p< 0.001) grade 3 or 4 toxicities were hematological, gastrointestinal, metabolic, fatigue, pain and neurologic. At a median follow up of 50 months, there was a statistically significant prolongation of median progression free survival (18.3 vs 23.8 months, p=0.05) and overall survival (49.7 vs 65.6 months, p=0.03) in the *intraperitoneal group*. Quality of life was reduced in patients in intraperitoneal group before 4th cycle (p<0.001) and after 6 cycles (p=0.009). However, after 1 year of completion of treatment, quality of life in both the groups was similar.

COMMENTS

Intraperitoneal chemotherapy was first proposed in 1978 by Dedrick et al to maximize the drug delivery to the tumour site with aim to achieve higher tissue levels of chemotherapy drugs and to reduce systemic side effects[7]. Thus, the advantages of intraperitoneal chemotherapy are (i) sustained high concentration exposure of tumour cells (sites) to the chemotherapeutic agents compared to plasma concentration (10- to 20-fold for cisplatin and > 1,000-fold for paclitaxel).[8, 9] (ii) ovarian cancer generally remains confined to the peritoneal cavity throughout the course of the disease therefore, this route appears to be favorable for treatment of ovarian cancer (iii) pharmacokinetic advantage of intraperitoneal chemotherapy results due to barrier effect of the peritoneal lining which limits the systemic exposure of the drugs.[10] However, intraperitoneal route has certain limitations also e.g. (i) It is suitable only in optimally cytoreduced tumour wherein the residual disease is less than 5mm [11]. (ii) The procedure is cumbersome, time consuming and needs expertise in the field. (iii) There is non uniform spread of the drug in the peritoneal cavity due to postoperative adhesion formation and may not reach all the target lesions. (iv) The drug delivered through this route does not reach sites of disease outside peritoneal cavity. (v) Toxicity associated with intraperitoneal chemotherapy is high compared to conventional intravenous route.

Present study have shown statistically significant prolongation of progression free survival (p=0.05) and overall survival (p=0.03) for patients receiving chemotherapy via intraperitoneal route. There was 25 percent reduction in risk of death due to ovarian cancer. Prior to this study, 5 randomized trials have compared intravenous and intraperitoneal chemotherapy as primary therapy in ovarian cancer. [4,12-15] These have been summarized in Table-1. Albert et al [15] achieved significant improvement in median overall survival in intraperitoneal group but did not mention about progression free survival that gave rise to many queries. The next largest study was conducted by GOG, Southwestern Oncology Group and Eastern Oncology group also showed superior overall and progression free survival in intraperitoneal group of patients.[4] In this study, 2 cycles of high dose of intravenous carboplatin (AUC-9) were used to reduce the tumour volume before intraperitoneal therapy, which made the interpretation difficult. The remaining three trials[12-14] included small number of patients and did not show significant improvement in survival. Chemotherapy agents and regimens used in all these trials were different. Intraperitoneal taxol was used only in 2 randomized studies.[4, 5] though phase I study published in 1992 concluded that paclitaxel could be delivered by the IP route with both an acceptable toxicity profile and a major pharmacokinetic advantage for cavity exposure.[9] The amount of residual disease after debulking surgery also was different in all these studies (table 1).

Table 1: Randomized studies on intraperitoneal chemotherapy as first line in ovarian cancer.

Author	control arm	experimental arm	OSc (months)	OSe (months)	pvalue	PFSc (months)	PFSe (months)	pvalue
Armstrong et al[2] 2006(n=429)	IV paclitaxel+ IV cisplatin	IV paclitaxel+ IP cisplatin+ IP paclitaxel	49.7	65.6	0.03	18.3	23.8	0.05
Markman et al [3] 2001 (n=523)	IV paclitaxel+ IV cisplatin	IV carboplatin+ IV paclitaxel+ IP cisplatin	52	63	0.05	22	28	0.01
Yen et al [4] 2001(n=132)	IV cisplatin	IP cisplatin	48	43	0.469	-	-	-
Gadducci et al [5] 2000(n=113)	IV CAP	IP cisplatin+ IV Adriamycin+ IV ctx	51	67	0.13	25	42	0.14
Polyzos et al [6] 1999(n=90)	IV carboplatin	IP carboplatin	25	26	NS	19	18	NS
Alberts et al [7] 1996(n=654)	IV cisplatin+ IV ctx	IP cisplatin+ IV ctx	41	49	0.02	-	-	-

OSc-overall survival of control arm, **OSe**- overall survival of experimental arm,
PFSc-progression free survival of control arm, **PFSe**- progression free survival of experimental arm
Ctx-cyclophosphamide, **CAP**- cyclophosphamide+adriamycin+cisplatin, **NS**-not significant

One of the major limitations of intraperitoneal route is associated morbidity - catheter related infections, blockage, adhesion formation etc. This is depicted by the fact that less than half the number of the patients (42%) could complete assigned 6 cycles of therapy in intraperitoneal group in the present study. Side effects included catheter related complications, hematological, fatigue, abdominal pain, metabolic abnormalities and neuropathy that made quality of life worse during the therapy. Catheter related complications (40 out of 119) were main cause of discontinuation in 40 patients and these included – catheter infections (21), blocked catheter (10), leaking catheter (3), fluid leaking from vagina (1) and problems related to port access (5).[6] The timing of placement of catheter, whether it was placed during surgery or delayed until randomization did not have any relation with failure to complete 6 cycles of intraperitoneal chemotherapy (37% vs 41%). Patients whose debulking surgery included recto sigmoid and left colon resection failed to initiate intraperitoneal chemotherapy when compared to patients who did not undergo this procedure (16% vs 5%, p=0.012).

The possible reasons for higher toxic events in the intraperitoneal group are (i) increased dose of cisplatin (100mg/m2), which gave rise to significantly increased gastrointestinal and neurological toxicity. (ii) intraperitoneal paclitaxel on day 8.Though the peritoneal clearance of paclitaxel is thought to be very slow, it was detectable in the plasma after intraperitoneal administration.

There are few modifications in the study design suggested to make intraperitoneal route more acceptable and reduce toxicities (a) reduction of dose of cisplatin from 100mg/m^2 to 75mg/m^2 (b) use of carboplatin instead of cisplatin because of better toxicity profile (c) administration of intravenous paclitaxel over 3 hours instead of 24-hour infusion that reduces the myelotoxicity. (d) use of single lumen venous access device attached to subcutaneous port that reduces fibrous sheath formation (e) avoiding insertion of peritoneal device at the time of left colon or recto sigmoid resection to prevent infections of the catheters. It is not known whether these modifications will preserve the survival advantage shown in the present study. This can be answered by more

randomized studies aiming to reduce toxicities and at the same time maintaining the survival advantage of intraperitoneal group.

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