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Intraperitoneal chemotherapy as consolidation strategy for advanced ovarian cancer

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INTRODUCTION Chemotherapy has been increasingly utilized as a primary treatment for epithelial ovarian tumors. It has been shown that alkylating agents are useful in the treatment of ovarian cancer. The response rates range from 11 to 67% and the median survival time is aproximately 14 months. The overall 5-year survival is less than 10%. Several non-alkylating drugs have shown activity in ovarian cancer patients. Among these drugs cisplatin appears to be more effective than alkylating agents, producing response rates of about 50% or more. The combination chemotherapy without cisplatin as initial treatment gives response rates ranging from 5 to 50% and a median survival time of approximately 14 months. These data suggest that combination regimens without cisplatin are not superior to alkylating agents. Cisplatin-based combination chemotherapy regimens have produced response rates of 60 to 80% and a median overall survival of approximately 20 months. Combination chemotherapy regimens containing cisplatin have been shown to produce higher response rates and in some studies, have produced a statistically significant prolongation of survival compared to drug regimens without cisplatin. A recent meta-analysis addressing this comparison in 1,400 patients revealed a strong trend in favor of platinum-containing combinations with respect to response, but not survival (1). Some have argued that single-agent cisplatin is equally effective and less toxic than platinum-containing combinations. This meta-analysis, however, suggests that the combination confers a 15% survival advantage over the use of single-agent platinum. This meta-analysis also showed that carboplatin and cisplatin are equivalent in terms of survival (1). However, two recent studies, while confirming that carboplatin and cisplatin when combined with cyclophosphamide have comparable recurrence rates, disease-free intervals and survival rates, show carboplatin to have a more favorable therapeutic index (2-3).

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The *Gynecologic Oncology Group (GOG)* (4) has conducted a randomized, phase III clinical trial comparing paclitaxel and cisplatin (TP) with cyclophosphamide and cisplatin (CP) in suboptimally debulked (>1 cm residual mass) stage III and IV patients who had no prior chemotherapy. There was a statistically significant improvement in the clinical response rate in the TP arm (73%) versus the CP arm (60%). Differences in surgically documented complete response were not statistically significant (20% for CP and 26% for TP). Median survival was also significantly better in the TP arm (24 months versus 38 months; $P = 0.001$). TP is now considered to be the preferred combination regimen. A confirmatory trial has been run in Europe and Canada. The main difference between this trial and the *GOG* trial was a different dose-schedule of paclitaxel (175 mg/sqm as a 3-hour infusion instead of 135 mg/sqm) (5). The data not yet published confirmed the *GOG* trial with greater neurotoxicity in the paclitaxel arm.

Although combination chemotherapy allows a high clinical response rate, only 30-40% of patients are in pathologic complete remission, as confirmed by second-look laparotomy (1, 6). Depending on risk factors, 30-60% of pathologic complete remission patients experience relapse during the first 2 years (7-8).

INTRAPERITONEAL CHEMOTHERAPY The relapse after a pathologic complete remission depends on some prognostic factors: initial stage, extend of residual disease after primary cytoreductive surgery and performance status (9-10). Initial disease and sites of relapse are in most cases confined to the abdomen or to the pelvis or both, so that intraperitoneal treatment is a logical approach.

The pharmacologic advantage of intraperitoneal chemotherapy has been carefully studied and confirmed in numerous clinical trials. Pharmacologic studies on a variety of compounds have shown that a large concentration gradient exists between the peritoneal fluid and the plasma following intraperitoneal administration, and *Beller et al.* (11) concluded that "as a result, the peritoneal surfaces are exposed to higher drug concentrations for longer periods of time when compared with plasma concentrations". This way, it is possible to use significantly higher doses of intraperitoneal chemotherapy without excessive sistemic toxicity. Theoretically, intraperitoneal chemotherapy allows a very high dose effect that might overcome resistance to the lower dose intravenous

cisplatin-based chemotherapy. High doses of intraperitoneal chemotherapy became a method of dose intensification and can be compared to bone marrow transplantation or high-dose intravenous chemotherapy with growth factor protection.

The dose-intensity analysis of chemotherapy regimens in ovarian cancer made by *Levin* and *Hryniuk* (12) shows: a significant correlation between response rates and average relative dose intensity; a significant correlation between median survival time of the entire group and dose intensity; cisplatin was the only drug for which clinical response correlated with the individual drug relative dose intensity and only in the ARDI 0.40 to 0.80.; cisplatin was also the only drug for which there was a significant correlation between relative dose intensity and survival in the 0.40 to 0.80 ARDI.

Intraperitoneal chemotherapy in ovarian cancer has been investigated for more than 20 years. A large number of clinical trials with intraperitoneal chemotherapy have been published indicating that there are subgroups of patients who may benefit from this administration technique. *Howell et al.* (13) summarized the results of a number of trials with intraperitoneal cisplatin and concluded that some patients achieved prolonged survival, especially when treated for small residual disease. The better results seen with small residual disease (≤ 2 cm) may be explained by better tumor penetration of cisplatin administered into the peritoneal cavity.

A renewed interest for intraperitoneal chemotherapy of ovarian cancer was initiated by the results of a large randomized phase III study which showed that the intraperitoneal route of administration was associated with longer survival and less toxicity as compared with the i.v. administration in patients with small-volume residual ovarian cancer (14).

INTRAPERITONEAL CHEMOTHERAPY AS CONSOLIDATION TREATMENT IN PATHOLOGIC COMPLETE REMISSION There is no consensus about the treatment of patients with ovarian cancer in pathologic complete remission after second-look surgery. The main options are: wait-and-see; maintenance therapy using three to six more cycles of the same induction chemotherapy; whole abdominal radiation therapy; high-dose chemotherapy followed by autologous bone marrow transplant; intraperitoneal chemotherapy.

None of these modalities have proved a clear and definitive advantage in terms of disease-free survival or survival, and there are no published results of randomized comparative studies in this field.

Concerning wait-and-see, in 41 patients in pathological complete remission *Neijt* (6) reported a 5-year survival rate of 42% and *Rubin et al.* (15) in a identical group of 91 patients observed 44% of recurrence rate at 5 years.

In respect of maintenance therapy using the same induction chemotherapy, *Hakes et al.* (16) reported, in a randomized trial comparing 5 to 10 cycles of cisplatin-based combination chemotherapy, no statistical difference in terms of disease free survival or survival. On the other hand, the results of the whole abdominal radiation therapy are conflicting. *Fuks et al.* (17) in a series of stage III pathological complete remission patients, reported that the whole abdominal radiation therapy did not enhance the cure rate. *Menczer et al.* (18), compared the outcome in two non-randomized groups of ovarian cancer patients in complete clinical remission who had minimal or no residual disease at second-look laparotomy. One group was treated after the reexploration with cisplatin intraperitoneal chemotherapy, the other one with abdominopelvic irradiation. The data of this study seem to suggest that the survival and the progression free interval duration of patients in complete clinical remission, who, subsequent to second-look laparotomy, were treated with intraperitoneal cisplatin chemotherapy are better than that of patients treated by abdominopelvic irradiation. This difference was only statistically significant in patients with a negative second-look laparotomy. Two randomized trials try to clarify the role of the whole abdominal radiation after second-look in ovarian cancer patients responding to surgery and chemotherapy. An *Italian group* (19) presented the results of a randomized study in which advanced ovarian cancer patients with pathologically confirmed complete response or with minimal residual disease after second-look (<2 cm) were treated with whole abdominopelvic radiotherapy or with three additional courses of the same chemotherapy that induced the response. With a median follow-up of 22 months the analysis of the results shows: the disease progression was observed in 11 of 20 patients (55%) treated with radiotherapy and in 6 of 21 patients (28.5%) treated with chemotherapy (p 0.08); the disease-related deaths occurred in 9 patients in the radiotherapy arm (45%) and in 3 patients (14.2%) in the chemotherapy arm (p 0.02). In conclusion, the chemotherapy was more effective than radiotherapy in controlling disease progression after surgery and front-line chemotherapy in patients with no or minimal residual disease at second-look. The second trial comes from the *North Thames Ovary Group Study* (20) with the aim of determining, in a randomized trial of advanced ovarian carcinoma, whether consolidation therapy with whole abdominal radiotherapy after chemotherapy improves survival and disease-free survival compared with the same continued chemotherapy (5 courses of carboplatin). All patients received, before response evaluation and after initial surgery, five monthly courses of carboplatin. The data reported don't show any significant difference between the two groups in terms of overall survival or progression-free survival. There

was also no difference in survival among patients in whom no residual disease was found at second-look.

In a *Norwegian Radium Hospital study* (21), 50 patients with negative second-look findings were assigned randomly to receive intraperitoneal 32P or no treatment and the results of the log-rank test for differences in survival distributions between the two groups were not significant or even suggestive of a prolonged survival in the 32P arm.

"High-dose chemotherapy" with autologous bone marrow transplant or PBSC support as consolidation treatment in pathological complete remission patients is still under investigation.

There are a few studies concerning "intraperitoneal consolidation chemotherapy" for pathological complete remission patients. *Beller et al.* (11) reported a nonrandomized study with a group of 75 patients. All of them were classified as having stage II-IV epithelial ovarian cancer at *New York University-Bellevue Medical Center*. After initial tumor reduction surgery, patients received a total of 3 to 4 cycles of i.v. cisplatin (20 mg/m^2 daily for 5 days) and i.v. cyclophosphamide (600 mg/m^2 on day 4). On completion of this first phase, patients were evaluated by noninvasive modalities and 53 (75%) had complete clinical response and were eligible for a consolidation treatment, with six cycles of intraperitoneal cisplatin (60 mg/m^2 day 1) and i.v. cyclophosphamide (600 mg/m^2 day 2). Fortynine patients entered in the second phase of chemotherapy and 20 (41%) achieved a pathological complete remission at second-look laparotomy. The authors concluded that the combination of intraperitoneal cisplatin and i.v. cyclophosphamide is feasible with acceptable toxicity but its impact on response and survival is limited to only "good-prognosis" patients. The consolidation treatment with intraperitoneal cisplatin in first-line did not appear to have major impact on the survival of all treated patients when compared with historical control series.

Menczer et al. (22) reported a nonrandomized study with a group of 25 patients receiving three intraperitoneal cisplatin (200 mg/m^2) cycles after surgery, 5-12 cycles of systemic cisplatin-based chemotherapy and negative second-look surgery, compared with 12 patients undergoing no further treatment. At reexploration, 17 out of 25 patients had a pathological complete response. There was a trend for better survival in the intraperitoneal group compared with the no treatment group. There was no difference in the duration of the progression-free interval.

Dufour et al. (23) included 50 patients with stage II-IV ovarian cancer in a phase II study. All patients underwent initial cytoreductive surgery followed by 6 cyclophosphamide, doxorubicin and cisplatin cycles. All patients were in pathological complete remission as confirmed by second-look laparotomy. Consolidation treatment consisted of 20 mg intraperitoneal mitoxantrone every 3 weeks for six cycles. With a median follow-up of 2 years, the 5-year predicted survival was 60% and the disease-free survival rate was 47%. Patients with no or microscopic residual disease after initial surgery had a better 5-year disease-free survival rate (76%) than those with macroscopic residual disease (31%). Toxicity was limited to mild abdominal pain not requiring dose reduction.

The *E.O.R.T.C. Gynecological Cancer Cooperative Group* started in 1987 a randomized phase III study in ovarian cancer patients with pathological complete remission after platinum-based induction chemotherapy and cytoreductive surgery comparing intraperitoneal cisplatin versus no further treatment. The objective of the study is to evaluate the effect of intraperitoneally administered maintenance chemotherapy on survival in patients who are already in complete remission at restaging laparotomy. It was foreseen to include 312 patients in both arms, but till now the trial is running slowly and that number of patients was not yet achieved and there are no published data. The results of this trial will be very important and hopefully will give guidelines concerning the place of the intraperitoneal chemotherapy with cisplatin as a consolidation treatment of advanced ovarian cancer patients in remission after cytoreductive surgery and a front-line cisplatin-based chemotherapy.

REFERENCE

1. Advanced Ovarian Cancer Trialists Group . Chemotherapy in advanced ovarian cancer : an overview of randomised clinical trials. BMJ 1991; 303:884-893.

2. Alberts DS, Green S, Hannigan EV et al. Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stage III and IV ovarian cancer. J Clin Oncol 1992; 10:706-717.

3. Swenerton K, Jeffrey J, Stuart G, et al. Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer : a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1992; 10:718-726.

4. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patienta with stage III and stage IV ovarian cancer. N Engl J Med 1996; 334:1-6.

5. Piccart MJ, Bertensen K, Stuart G, et al. Is cisplatin-paclitaxel the standard in first-line treatment of advanced ovarian cancer ? EORTC-GCCG, NOCOVA, NCI-C and Scottish intergroup experience Proc Am Soc Clin Oncol 1997; 16:1258 (abstract).

6. Neijt JP. Treatment of advanced ovarian cancer : 10 years of experience . Ann Oncol 1992; 3:17-27.

7. Podczaski E, Manetta A, Kaminski P, et al. Survival of patients with ovarian epithelial carcinomas after second look laparotomy. Gynecol Oncol 1990; 36:43-47.

8. Neijt JP, ten Bokkel Huinink WW, van der Burg MEL et al. Complete remission at laparotomy: still a gold standard in ovarian cancer? Lancet 1986; 1:1028.

9. Maloisel F, Dufour P, Bergerat J, et al. Resultats d'une chimiotherapie¹ base de cisplatine et analyse des facteurs prognostiques dans les cancers de l'ovaire : a propos de 106 cas. Bull Cancer 1989; 76:1083-1093.

10. Lund B, Williamson P. Prognostic factors for overall survival in patients with advanced ovarian carcinoma. Ann Oncol 1991; 2:281-287.

11.- Beller U, Speyer J, Colombo N, et al. Consolidation with intraperitoneal cisplatin in first-line therapy of advanced ovarian cancer. J Clin Oncol 1991; 9:809-817.

12. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. J Clin Oncol 1987; 5:756-767.

13. Howell S B, Zimm S, Markman M, et al. Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. J Clin Oncol 1987; 5:1607-1612.

14. Alberts DS, Liu PY, Hannigan EV, et al. Phase III study of intraperitoneal (IP) cisplatin (CDDP) / intravenous (IV) cyclophosphamide (CPA) vs IV CDDP / IV CPA in patients (PTS) with optimal disease stage III ovarian cancer : a SWOG-GOG-ECOG intergroup study (INT 0051). Proc Am Soc Clin Oncol 1995; 14:760 (abstract).

15. Rubin SC, Hoskins WJ, Saigo PE et al. Prognostic factors for recurrence following negative second-look laparotomy in ovarian cancer patients treated with platinum based chemotherapy. Gynecol Oncol 1991; 42:137-141.

16. Hakes T, Chalas E, Hoskins WJ, et al. Randomized prospective trial 5 versus 10 cycles of cyclophosphamide, doxorubicin and cisplatin in advanced ovarian carcinoma. Gynecol Oncol 1992; 45:284-289.

17. Fuks Z, Rizel S, Brian S. Chemotherapeutic and surgical induction pathological complete remession and whole abdominal irradiation for consolidation does not enhance the cure of stage III ovarian carcinoma. J Clin Oncol 1988; 6:509-516.

18. Menczer J, Ben-Baruch G, Modan M, et al. Intraperitoneal cisplatin chemoyherapy versus abdominopelvic irradiation in ovarian carcinoma patients after second-look laparotomy. Cancer 1989; 63:1509-1513.

19. Bruzzone M, Repetto L, Chiara S, et al. Chemotherapy versus radiotherapy in the management of ovarian cancer patients with pathological complete response or minimal residual disease at second-look. Gynecologic Oncology 1990; 38:392-395.

20. Lambert HE., Rustin GJS, Gregory WM, et al. A randomized trial comparing single-agent carboplatin with carboplatin followed by radiotherapy for advanced ovarian cancer : a North Thames Ovary Group Study. J Clin Oncol 1993; 11:440-448.

21. Vergote IB, Winderen M, De Vos LN, et al. Intraperitoneal radioactive phosphorus therapy in ovarian carcinoma. Analysis of 313 patients treated primarily or at second-look laparotomy. Cancer 1993; 71:2250-2260.

22. Menczer J, Ben-Baruch G, Rizel S, et al. Intraperitoneal chemotherapy versus no treatment in patients with ovarian carcinoma who are in complete clinical remission. Cancer 1992; 70:1956-1959.

23. Dufour P, Bergerat J-P, Barats J-P, et al. Intraperitoneal mitoxantrone as consolidation treatment for patients with ovarian carcinoma in pathologic complete remission. Cancer 1994; 73:1865-1869.