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Objective : *To present the overview of current role of platinum-based chemotherapy in advanced ovarian cancer.*

Setting : *A computerized search of articles published through December 1996 was performed on the Medline and Cancerlit data base. Additional sources were identified through cross-referencing.*

Method : *All identified references were reviewed with particular attention to their relevance to platinum-based chemotherapy in advanced ovarian cancer.*

Conclusion : *Platinum-based chemotherapy remains the standard treatment in advanced ovarian cancer. Carboplatin appears to be equivalent in activity to cisplatin in the treatment of ovarian cancer.*

Key words : *Cisplatin, Carboplatin, Platinum, Ovarian cancer.*

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วัตถุประสงค์ : *เพื่อนำเสนอบทบาทปัจจุบันของเคมีบำบัดกลุ่มพลาตินั่มในการรักษามะเร็งรังไข่ระยะลุกลาม*

วิธีการวิจัย : *รวบรวมผลการศึกษาเกี่ยวกับเคมีบำบัดกลุ่มพลาตินั่มในการรักษามะเร็งรังไข่ระยะลุกลามจากการสืบค้นทางคอมพิวเตอร์ในระบบข้อมูล Medline และ Cancerlit จนถึงเดือนธันวาคม 2539 ประมวลเปรียบเทียบข้อมูลและนำเสนอตลอดจนวิเคราะห์ผลการศึกษาดังกล่าว*

สรุป : *เคมีบำบัดกลุ่มพลาตินั่ม ยังเป็นกลุ่มยามาตรฐานหลักในการรักษามะเร็งรังไข่ระยะลุกลาม Carboplatin มีประสิทธิภาพเทียบเท่า Cisplatin ในการรักษามะเร็งรังไข่*

For the majority of patients presented with advanced ovarian cancer (stage III or IV) the standard treatment has been cytoreductive surgery (or debulking surgery) to remove the primary tumor as well as the associated metastatic disease, and to determine accurately the extent of disease, followed by combination chemotherapy. However, with advanced disease patients, the volume of residual disease is a critical determinant of patient response to the chemotherapy as well as their survival.[1] Systemic chemotherapy is the standard treatment for advanced epithelial ovarian cancer.[2] Oral single-agent alkylating therapy had been used for many years[3] but the introduction of cisplatin in the latter half of the 1970s changed the therapeutic approach for the most frequently used treatment regimen in the United States. Recently, paclitaxel has become available, and its combination with other drugs is now in use. The use of single-agent chemotherapy which is less toxic for metastatic epithelial ovarian cancer is generally reserved for patients whose overall physical condition precludes the use of more toxic combinations therapy, such as elderly or delibitated patients.

In this article, we will focus on the current role of platinum-based chemotherapy in advanced ovarian cancer treatment.

Combination Chemotherapy

The relatively large number of active drugs available for epithelial ovarian cancer treatment points to the potential for the development of effective combination therapy. Combination chemotherapy has been shown to be superior to single-agent therapy in most patients with advanced ovarian cancer.[4] The first study to show the benefits with combination therapy compared a Hexa-CAF (hexamethylmelamine, Cytoxan, methotrexate, 5-FU) regimen with melphalan and showed that the response rates and the median survival rates with the combination regimen were better than with the single drug.[5] The Hexa-CAF regimen produced a complete response rate of 33% with a median survival of 29 months, compared with 16% and 17 months, respectively, for melphalan. A variety of combination chemotherapeutic regimens have been studied for the treatment of advanced epithelial ovarian cancer. A summary of the most common regimens is presented in Table 1.

Platinum-based Combination Chemotherapy

The platinum compounds remain one of the most active drugs in epithelial ovarian cancer treatment since they were first introduced into clinics in the late 1970s.[6] Cisplatin, the most extensively studied platinum compound has clear-cut activity in patients with no prior chemotherapy, as well as in those who have received prior alkylating agents.[7,8] Subsequently, it has been incorporated into combination chemotherapeutic regimens with other active drugs, like cyclophosphamide, hexamethylmelamine, and doxorubicin. One such regimen, CHAP (Cytoxan, hexameth-ylmelamine, adriamycin, cisplatin), was

Table 1. Chemotherapeutic regimens for advanced ovarian cancer.

	Regimen	Interval
PC	Cisplatin (75-100 mg/m^2) Cyclophosphamide (650-1000 mg/m^2)	Q 3 weeks
CC	Carboplatin (AUC = 5-7) Cyclophosphamide (600 mg/m^2)	Q 4 weeks
PAC	Cisplatin (50 mg/m^2) Adriamycin 50 mg/m^2 Cyclophosphamide (500 mg/m^2)	Q 3-4 weeks
CHAP	Hexamethylmelamine 150 mg/m^2 orally days 1-14 Cyclophosphamide 350 mg/m^2 IV day 1 and day 8 Adriamycin 20 mg/m^2 IV day 1 and day 8 Cisplatin 60 mg/m^2 IV day 1	Q 3-4 weeks
PT	Cisplatin (75-100 mg/m^2) Taxol (135-210 mg/m^2)	Q 3 weeks
CT	Carboplatin (starting dose, AUC = 5) Taxol (135-175 mg/m^2)	Q 3-4 weeks

AUC = area under the curve

shown to be active and generally tolerable.[9] Because of the toxicity of hexamethylmelamine, particularly the depression that some patients experience with the drug, many oncologists omitted that agent.

In a meta-analysis on studies of patients with advanced stage disease, those given cisplatin-containing combination chemotherapy were compared with those treated with regimens that did not include cisplatin.[4] Survival differences between the groups were noted for 2 to 5 years, with the cisplatin group having a slight survival advantage, but the difference disappeared by 8 years.[4] At a consensus meeting on the treatment of advanced ovarian cancer, there was agreement that after appropriate cytoreductive surgery, platinum-based chemotherapy yields superior response rates, progression-free survival, and superior survival rates.[10]

The addition of doxorubicin to cisplatin and cyclophosphamide regimens is another interesting issue. The recent consensus[11] is that

either cyclophosphamide (750 mg/m^2) plus cisplatin (75 mg/m^2) every 3 weeks or cyclophosphamide (500 mg/m^2) plus doxorubicin (50 mg/m^2) plus cisplatin (50 mg/m^2) (CAP) every 3 weeks is acceptable standard therapy. However, four prospective randomized trials[12-15] comparing cisplatin and cyclophosphamide with the CAP regimen failed to show statistically significant differences in overall survival. The largest of the above trials was that of the Italian Cooperative Gynecologic Oncology Group (GICOG), which randomized 529 patients to receive CAP, cisplatin/cyclophosphamide (PC), or single-agent cisplatin[12] No statistical difference was seen in overall survival (5 years minimum follow-up) among the three groups. Meta-analysis of the above four trials[16] revealed a 6-year survival advantage of 7% in patients receiving the doxorubicin containing regimen, but it remains unclear whether the benefit was a result of doxorubicin or the greater dose intensity reached by adding it. Gadducci et al reported their update data which revealed no significant difference in PFS between the PC and CAP regimens. However, there is a trend in favor of the CAP regimen among patients with residual disease >2 cm.[17] Because of the cardiotoxicity of doxorubicin, it would be desirable to omit the drug if overall response rates were not significantly changed. A large prospective randomized Dutch study of CHAP versus PC showed that response rates and median survival rates were almost identical.[18] Because the toxicity of PC was significantly less than that of the four-drug treatment, it was concluded that PC should be considered the treatment of choice.

Another controversial issue is the number of cycles of chemotherapy to be given. Most studies report 5 to 10 courses of treatment, and it is generally agreed that most response occurs within four courses of chemotherapy. Two prospective randomized trials failed to demonstrate any significant benefit for more prolonged treatment.[19,20] The current recommendation is to give at least six courses of treatment. There is no evidence so far to show that additional treatment produces any benefit.

Cisplatin Dose Intensity

The importance of dose intensity (mg/m^2/time period) in relation to clinical outcome in ovarian cancer has been analyzed by several investigators. At present, the published data from the randomized trials of dose intensity for ovarian cancer have failed to confirm a benefit in favor of the dose-intense approach.[21-29] The large Scottish trial[21] showed a difference in survival but included in its population optimally debulked patients with stage IC to IV disease. Recently, the mature results of this group showed the overall survival rates for high-dose and low-dose arm were 32.4% and 26.6%, respectively, and the overall relative death rate was 0.68 (P=0.043).[22] This represents a reduction in overall benefit with longer follow-up compared with the first 2 years of study (relative death rate of 0.52).

Toxicity, particularly neurotoxicity, was still evident in the fourth year (10/31 on HD compared with 1/24 on LD). A Hong Kong trial included stage III to IV patients who showed improved survival with high-dose regimens, but the patient population was small. [23]

The Gynecologic Oncology Group (GOG) trial of patients with suboptimal stage III disease failed to demonstrate survival advantage for the high-dose chemotherapy arm.[24] However, it is important to note that the final assessment of clinical response was based on a relatively small subset of patients with measurable disease (34%), and that in this study the high-intensity arm consisted of only four courses of chemotherapy (Table 2).[12,20-28] It is possible that a greater increase in dose intensity was required to produce clinically meaningful improvement in patients with advanced disease. A critical problem; however, with evaluation of dose intensity in ovarian

Table 2. Randomized trials of cisplatin/cyclophosphamide dose intensity.

Group	Disease stage	Number of patients	Drug Regimens	Dose intensity	Cumulative dose	Assigned increase in dose intensified arm	Results
Hong Kong (23)	Stage III/IV	60	Cisplatin 100 mg/m^2 + CTX 1,000 mg/m^2 vs cisplatin 50 mg/m^2 + CTX 1,000 mg/m^2 x 6 cycles	+	+	x 2	3-year survival rates: higher dose = 60% lower dose = 30%
GOG (24)	Untreated suboptimal stage III/IV	458	Cisplatin 100 mg/m^2 +CTX 1,000 mg/m^2 x 4 vs cisplatin 50 mg/m^2 + CTX 500 mg/m^2 x 8	+	-	x 2	Median survival duration : higher dose = 21.9 m. lower dose = 18.9 m.
Scottish (21)	Stage I-IV	165	Cisplatin 100 mg/m^2 +CTX 750 mg/m^2 vs Cisplatin 50 mg/m^2 +CTX 750 mg/m^2 x 6 cycles	+	-	x 2	Median survival duration: higher dose = 28.5 m. lower dose = 17.2 m
Italian (12)	Stage III/IV	296	Cisplatin 75 mg/m^2 every 3 wk x 6 vs cisplatin 50 mg/m^2 every wk x 9 cycles	+	-	x 2	Median survival duration: higher dose = 36 m. lower dose = 33 m.
Danish (20)	Stage II-IV	78	AUC escalation from: 3-8 mg/ml/min	+	+	AUC x 4 vs AUC x 8	Higher PCR survival too early for analysis

CTX = cyclophosphamide, PCR = pathologic complete response

cancer is that multiple chemotherapy related toxicities preclude marked increases in dose intensity for prolonged periods.

Those studies that focused on patients with suboptimally debulked disease consistently reported negative results regarding statistically significant improvements in response rates and overall survival. Studies focusing on patients with optimally debulked disease have reported positive and negative points both in terms of response rate and overall survival. Dose intensity should thus be more likely to lead to enhanced survival in small-volume disease.

Carboplatin versus Cisplatin

Carboplatin, the second-generation platinum analogue, was developed and introduced to have less toxicity than its parent compound, cisplatin. Carboplatin was shown to have lower toxicity with fewer gastrointestinal side effects, especially nausea and vomiting, less neurotoxicity, less nephrotoxicity and less ototoxicity but more thrombocytopenia than cisplatin.[30-33]

The issue of carboplatin VS. cisplatin remains one of the most common concerns in treating ovarian cancer. A meta-analysis was conducted by the Advanced Ovarian Cancer Trialist Group (AOCTG)[4] that incorporated data from over 2,000 patients. When it compared carboplatin and cisplatin treatment groups, it failed to demonstrate any significant differences in overall survival between the two groups, and a similar conclusion came from two large North American trials: a trial by the Southwest Oncology Group[32] (342 patients with stage III or IV disease randomized to receive cisplatin, 100mg/m^2, plus cyclophosp-hamide, 600 mg/m^2 , or carboplatin, 300 mg/m^2, plus cyclophosphamide 600 mg/m^2) and a trial by the National Cancer Institute of Canada[33] (447 patients randomized to receive cisplatin 75 mg/m^2, plus cyclophosphamide vs. carboplatin/cyclophosphamide). All three of these trials failed to demonstrate a significant difference in overall survival rates, though the carboplatin regimen was found to have a better therapeutic index and to produce a better quality of life.[32,33] In contrast, a recent French trial[34] involving 144 patients with stage III or IV disease who received either cisplatin or carboplatin demonstrated very different results, as seen in[30,32-37]. The doses of cyclophosphamide (500 mg/m^2) and doxorubicin (40 mg/m^2) were the same in both groups. The pathologic complete remission and overall response rates were significantly higher in the cisplatin arm than in the carboplatin arm (33% vs. 15% and 73% vs. 47%, respectively). The medial survival time was 27.9 months for the cisplatin arm and 20.6 months for the carboplatin arm. The actual delivered dose intensity of the drugs in the two arms was not reported.[34]

At the recent National Institutes of Health Consensus Conference on Ovarian Cancer,[38] it was concluded that data from mature randomized clinical trials have indicated that the combination of carboplatin and cyclophosphamide is effective

Table 3. Carboplatin vs Cisplatin in combination chemotherapy for advanced ovarian cancer: treatment results.

Group (ref)	No.of patients	Carb/Cis Dose (mg/m^2)	Carb/Cis PDI ($mg/m^2/wk$)	Combine w/Drug	SOD(%)	Carb/Cis PCR	Carb/Cis Median PFS (mos.)	Carb/Cis Median surv (mos.)
NCIC (33)	417	300/75	75/18.75	CTX	59 (1)	11/15	13.4/12.9	25.8/23.8
EORTC (30)	342	350/100	70/20	DOX CTX HMM	63 (2)	23/27	13.1/16.8	22.7/24.6
SWOG (33)	291	300/100	75/25	CTX	100 (1)	8/7	N/A	19.8/17.4
GONO (35)	164	200/50	50/12.5	DOX CTX	66 (1)	14/20	15.5/13.2	23.1/22.6
ARTAC (34)	144	300/75	75/18.75	DOX CTX	N/A	10/25	N/A	20.6/27.9
NCCTG /Mayo (36)	103	150/60	37.5/15	CTX	35 (1)	N/A	12.0/17.0	20.0/27.0
UK (37)	56	300/100	75/25	CTX	77 (1)	N/A	24.0/13.0	24.0/19.0

PDI = Planned dose intensity, 20 $mg/m^2/day$* 5, DOX: doxorubicin; CTX: cyclophosphamide;
HMM : hexamethylmelamine; SOD: suboptimally debulked; PCR: pathologic complete response;
PFS : progression-free survival; N/A: not available.
(1) : lesions>2 cm; (2): lesions>1 cm.

therapy, and the substitution of carboplatin for cisplatin leads to reduced toxicity.

In summary, platinum-base chemotherapy remains the standard treatment in advanced ovarian cancer. Carboplatin appears to be equivalent in activity to cisplatin in the treatment of ovarian cancer.[6,38-40] The two-drug combination of cyclophosphamide and cisplatin or carboplatin results in 60% to 80% overall response rate and 40% to 50% clinical complete response.

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