One Year Maintenance of Carboplatin in Patients with Epithelial Ovarian Cancer – A Phase II Study

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Abstract

Background: The 5 year survival rate in patients with advanced epithelial ovarian cancer is 25–40% and treatment is mainly palliative once the disease recurs.

Objectives: To determine the time to progression, overall survival and toxicity of 1 year maintenance treatment with carboplatin in women with advanced EOC after achieving complete remission with platinum-based combination chemotherapy.

Methods: Twenty-two women with epithelial ovarian cancer stage III-IV previously treated with platinum-based combinations who had achieved complete remission evidenced by symptoms, pelvic examination, computerized tomography and serum CA-125, were assigned to the study protocol consisting of: carboplatin of AUC=6, three cycles every 2 months, followed by two cycles once every 3 months for a total of five courses over 1 year.

Results: Median follow-up in the 22 patients was 83 months (range 18–133 months), median disease-free survival was 36 months (range 2.5–126.4, 95% confidence interval 16.39–56.34). The 5 year survival was 59.7% with a mean overall survival of 83 months (range 18–133, 95% CI 39.11-127.29). Eleven patients have relapsed and died, 11 are alive, 6 are still in complete remission, and 5 are alive with recurrent disease. Grade III-IV toxicity was shown in some of the patients, anemia in 9%, thrombocytopenia in 9%, fatigue in 4.5%, and hypersensitivity in 4.5%.

Conclusions: A 1 year extension of treatment with a single-agent carboplatin, administered to women with advanced EOC who had achieved complete recovery on platinum-based chemotherapy as their first-line therapy, has an acceptable toxicity. The disease-free survival and overall survival values noted in this study are encouraging and warrant further investigation.

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The 5 year survival rate of patients with advanced epithelial ovarian cancer is 25%–40% and treatment is mainly palliative once the disease recurs. Several methods have been and are being tested with the intention of increasing overall survival after standard surgery and chemotherapies consisting of platinum with or without a taxane agent. They include triple-agent combination chemotherapy, intraperitoneal consolidation therapy, and maintenance therapy. Prolonged disease-free survival by maintenance chemotherapy in platinum-sensitive patients was demonstrated by Eltabbakh et al. [1], and prolonged disease-free survival with non-conclusive effects on overall survival following 12 months of maintenance paclitaxel was reported by Markman et al. [2]. In our current study, we administered an additional year of carboplatin therapy to EOC patients who had responded with complete response to their first-line platinum-based therapy to determine whether it could prolong the time to progression as well as overall and disease-free survival with reasonable toxicity.

EOC = epithelial ovarian cancer
CI = confidence interval

Patients and Methods

We conducted this open non-randomized phase II trial on patients with stage III-IV epithelial ovarian cancer who were treated with 1 year of maintenance carboplatin after complete remission on cytoreductive surgery and platinum-based chemotherapy. Eligibility criteria included histologic confirmation of EOC or primary peritoneal carcinoma, previous exposure to cytoreductive surgery and complete remission after first-line

Table 1. Patient characteristics (n = 22)

Age (yrs)	
Median	60
Range	39–84
ECOG performance status	
0	8
1	10
2	4
FIGO stage	
Stage IIIb	2
Stage IIIc	17
Stage IV	3
Histologic type	
Serous papillary adenocarcinoma	11
Moderately differentiated adenocarcinoma	5
Poorly differentiated adenocarcinoma	6
Cytoreductive surgery	
Mass > 5 cm at diagnosis	7
Suboptimal debulking (> 2 cm)	5
Type of prior chemotherapy	
Caroplatin with cyclophosphamide	16
Carboplatin with paclitaxel	4
Carboplatin with doxorubicin with cyclophosphamide	1
Carboplatin	1
Schedule of prior chemotherapy	
Primary cytoreduction followed by chemotherapy	15
Neoadjuvant chemotherapy with interval debulking	7

chemotherapy. Additional requirements included an Eastern Cooperative Oncology Group performance status of ≤ 2 and a life expectancy of at least 3 months. All patients signed informed consent forms.

Twenty-two women with EOC who had been previously treated with platinum-based combinations were enrolled. Their characteristics are summarized in Table 1. Median age was 60 years (range 39–84 years), median ECOG performance status was 1 (range 0–2), EOC stage was III (n=19, 86%) or stage IV (n=3, 14%) at diagnosis. Of the 22 patient cohort, 7 (31%) had masses larger than 5 cm at diagnosis, and 5 (23%) had suboptimal debulking, i.e., cytoreductive surgery (residual of >2 cm). They had all achieved complete initial therapeutic response as assessed by clinical symptoms, computerized tomographic scan, and serum CA-125 measurements, and were assigned to the study protocol between 1991 and 1997 in the Department of Oncology.

The schedule was carboplatin of AUC=6 (area under the curve – Calvert formula), three cycles every 2 months followed by two cycles once every 3 months for a total of 1 year. Overall survival and disease-free survival were measured from the day maintenance treatment was initiated (within 6 weeks of the last chemotherapy session). Progression was defined as the appearance of a new lesion(s) on any imaging technique, clinical signs of recurrence or elevation of markers.

Primary chemotherapy consisted of carboplatin with cyclophosphamide in 16 of the 22 patients (73%), carboplatin with paclitaxel in 4 (18%), carboplatin with adriamycin and cytoxan in 1 (4.5%), and carboplatin alone in 1 (4.5%). Seven patients (32%) had received neoadjuvant chemotherapy followed by interval debulking and chemotherapy.

Results

As of February 2004, 22 patients (mean age 60 years, range 39–84) were available for evaluation of progression, survival and toxicity. The median follow-up was 83 months (range 18–133 months), the median disease-free survival (with 16 events) was 36 months (SE = 10.19, range 2.5–126.4 months, with 95% confidence interval 16.39–56.34, Kaplan-Meier plot) [Figure 1A]. The 5 year survival was 59.7% (SE = 11.1) with a mean overall survival (with 11 events) of 83 months (SE = 22.50, range 18–133 months, 95% CI 39.11–127.29, Kaplan-Meier plot) [Figure 1B]. Six patients are still alive in complete remission and five are alive with recurrent disease. Seventeen of the 22 completed all cycles of the protocol; 5 patients withdrew from the treatment early, 4 due to disease progression and one for non-compliance because of extreme fatigue. Four patients had dose modifications (carboplatin of AUC=5). No administrative delays were noted due to the long interval between cycles. Grade III-IV toxicity was due to anemia in two patients (9%), thrombocytopenia in two (9%), fatigue in one (4.5%), and hypersensitivity in one (4.5%) [Table 2].

ECOG = Eastern Cooperative Oncology Group

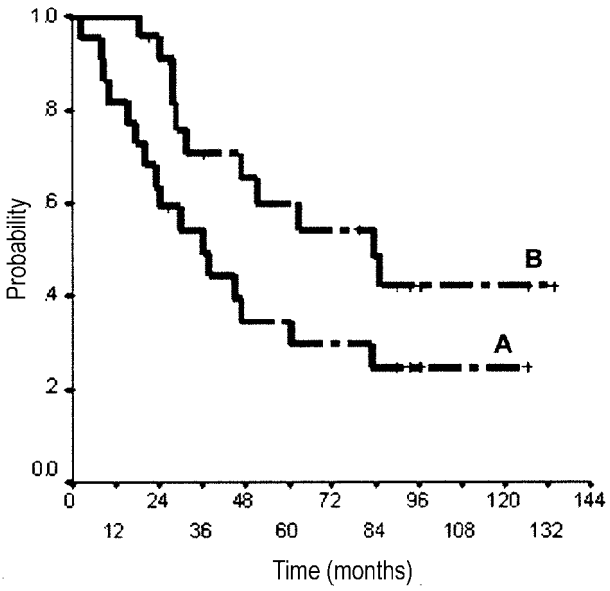

Figure 1. [A] Progression-free survival: Kaplan-Meier analysis of time from beginning of maintenance chemotherapy to disease progression. **[B]** Overall survival: Kaplan-Meier analysis of time from beginning of maintenance chemotherapy to death.

Table 2. Maintenance carboplatin-induced toxicity (n=22)

Grade III-IV toxicity	Percent (no.) of patients
Anemia	9% (2/22)
Thrombocytopenia	9% (2/22)
Fatigue	4.5% (1/22)
Hypersensitivity	4.5% (1/22)

Discussion

The 5 year survival rate among patients with EOC is 25–40% when discovered at stage III-IV, and despite a 60–80% response rate, more than 75% of those patients will have recurrence of the disease within 5 years of standard therapy, including cytoreductive surgery and platinum with or without taxane adjuvant chemotherapy [2–5]. Continuous efforts are underway to improve the overall survival rate of these patients. High dose chemotherapy did not bring the desired results [6–9], nor did consolidation with intraperitoneal chemotherapy [10]. Three-drug combinations ("triplets") are currently under investigation, including GOG 182 [11,12]. Maintenance chemotherapy – in similar groups of women who achieved complete remission on first-line chemotherapy – has been tried in small studies over the years and showed a tendency for prolonged disease-free survival. A recent phase III study by Markman and colleagues [13] compared 12 months of paclitaxel maintenance chemotherapy to 3 months of that treatment, and showed prolonged disease-free survival but gave no conclusive data for overall survival due to early cessation of the study when early results showed a significant disease-free survival in favor of the 12 cycles. The two essential questions that their study left unanswered are whether overall survival is also improved and whether the change in disease-free survival

is worth the chemotherapy's additional toxicity. The former question remains unanswered because the study was stopped. The enhancement in disease-free survival was a median of 7 months for 9 additional months of treatment; however, the final word is not yet out on this issue.

Our study evaluated the disease-free survival, overall survival, and toxicity of an additional year of maintenance carboplatin in a selected group that achieved complete remission after first-line platinum-based chemotherapy. This selected group was comparable to the one selected by Markman and colleagues [13] in their phase III randomized study. It must be pointed out that we had a relatively small patient cohort (22 patients) and it was a phase II and not a phase III study. We observed an acceptable degree of toxicity with relatively good disease-free and overall survival; this, despite the fact that over 75% of the patients were primarily treated with platinum-based chemotherapy that did not include taxanes and was supposedly an inferior protocol to that of platinum combined with taxane [3,4]. It could be that repeating the most important chemotherapy in EOC, i.e., a prolonged platinum-based protocol, might have further improved both disease-free and overall survival, and might have been even more effective had the primary therapy included taxanes. This theory and schedule of carboplatin maintenance administration warrant additional larger scale studies.

Conclusions

One year of additional treatment with a single agent carboplatin administered to a selected group of women with advanced EOC who had achieved complete recovery on platinum-based chemotherapy as first-line therapy suggests prolonged time to progression, overall survival, and 5 year survival with reasonable toxicity and warrants further investigation.

References

1. Eltabbakh GH, Piver MS, Hempling RE, Recio FO, Blumenson LE. Prolonged disease-free survival by maintenance chemotherapy among patients with recurrent platinum-sensitive ovarian cancer. *Gynecol Oncol* 1998;71:190–5.
2. Markman M, Bundy B, Alberts D, et al. Phase III trial of standard dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small volume stage III ovarian carcinoma: An intergroup trial (GOG, SWOG, ECOG). *J Clin Oncol* 2001;19:1001–7.
3. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1–6.
4. Piccart M, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699–708.
5. Muggia FM, Braly PS, Brady MF, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III and IV ovarian cancer: A Gynecologic Oncology Group study. *J Clin Oncol* 2000;18:106–15.
6. Stiff PJ, Veum-Stone J, Lazarus HM, et al. High-dose chemotherapy and autologous stem-cell transplantation for ovarian cancer: an autologous blood and marrow transplant registry report. *Ann Intern Med* 2000;133:504–15.
7. Levin L, Hryniuk W. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol* 1987;5:756–67.
8. Levin L, Simon R, Hryniuk W. Importance of multiagent chemotherapy regimens in ovarian carcinoma: dose intensity analysis. *J Natl Cancer Inst* 1993;85:1732–42.
9. McGuire WP, Hoskins WJ, Brady MF, et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 1995;13:1589–99.
10. Markman M, Reichman B, Hakes T, et al. Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: influence of a prior response to intravenous cisplatin. *J Clin Oncol* 1991;9:1801–5.
11. Bookman MA, Greer BE, Ozols RF. Optimal therapy of advanced ovarian cancer: carboplatin and paclitaxel vs. cisplatin and paclitaxel (GOG 158) and an update on GOG0 182-ICON5. *Int J Gynecol Cancer* 2003;13:735–40.
12. Copeland LJ, Bookman M, Trimble E. Gynecologic Oncology Group Protocol GOG 182-ICON5. Clinical trials of newer regimens for treating ovarian cancer: the rationale for Gynecologic Oncology Group Protocol GOG 182-ICON5. *Gynecol Oncol* 2003;90:S1–7.
13. Markman M, Liu PY, Wilczynski S, et al. Southwest Oncology Group; Gynecologic Oncology Group. Phase III randomized trial of 12 versus 3 months of single-agent paclitaxel in patients with advanced ovarian cancer who attained a clinically defined complete response to platinum/paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol* 2003;21:2460–5.

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