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SINGLE AGENT CARBOPLATIN VERSUS CARBOPLATIN PLUS PEGYLATED LIPOSOMAL DOXORUBICIN IN RECURRENT OVARIAN CANCER: FINAL SURVIVAL RESULTS OF A SWOG (S0200) PHASE 3 RANDOMIZED TRIAL

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Abstract

Objectives—Randomized phase 3 trials have demonstrated the utility of a regimen of carboplatin plus pegylated liposomal doxorubicin (PLD) in recurrent ovarian cancer, and have provided provocative data suggesting a substantially lower risk of carboplatin-associated hypersensitivity if PDL is delivered in combination with the platinum agent.

Methods—To further examine both of these clinically-relevant issues, the survival outcome (with longer follow-up) and hypersensitivity reaction profile of a previously reported phase 3 trial that compared single agent carboplatin (AUC 5) to carboplatin (AUC 5) plus PLD (30 mg/m²) delivered on an every 4-week schedule in recurrent ovarian cancer (SWOG 0200) were re-analyzed.

Results—In the limited number of patients (n=61) entered into this phase 3 study before closure by the SWOG Data Safety and Monitoring Committee due to insufficient accrual, there was an initially reported improvement in outcome associated with the combination regimen. With longer follow-up and additional events there is still a statistically-significant improved progression-free survival (median: 12 versus 8 months, p=0.02), but the previously observed impact of the two-drug regimen on overall survival is no longer apparent (median: 31 versus 18 months; p=0.2). While no

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Conflict of Interest Statement

Maurie Markman, M.D. – Consultant for Ortho-Biotech.

All other authors declare that there are no conflicts of interest.

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hypersensitivity reactions were reported in the carboplatin plus PLD arm (0/31), 9 of 30 patients (30%) of women randomized to single agent carboplatin experienced an allergic episode ($p=0.0008$), with 5 being $\geq$ grade 3 in severity.

Conclusion—Despite a favorable impact of carboplatin and PLD on progression-free survival in this trial, the effect on overall survival is not statistically significant. For currently unknown reasons, administering PLD with carboplatin appears to substantially reduce the incidence of platinum-associated hypersensitivity reactions.

INTRODUCTION

The results of both previously published, and more recently presented, phase 3 randomized trials have provided clinically-relevant data that can assist clinicians in their determination of optimal management for women experiencing recurrence of epithelial ovarian cancer [1–5]. In particular, two phase 3 studies have demonstrated the superiority of the delivery of a platinum-agent plus paclitaxel or carboplatin plus gemcitabine, compared to the administration of a non-paclitaxel containing platinum regimen or single agent carboplatin, respectively, in this clinical setting [1,2].

An additional phase 3 trial (Southwest Oncology Group study S0200) that compared single agent carboplatin to a regimen of carboplatin plus pegylated liposomal doxorubicin (PLD), that was unfortunately discontinued early due to inadequate accrual, also revealed a provocative improvement in progression-free survival associated with the 2-drug regimen (12 months versus 8 months; $p=0.03$), despite very limited patient numbers [4]. Further, at the time the results of this underpowered study were reported, there was an observed statistically-significant improvement in overall survival (26 months versus 18 months; $p=0.02$) [4].

Interest in the combination of carboplatin plus PLD in the treatment of recurrent ovarian cancer has been heightened by the results of a large phase 3 trial (CALPYSO) that directly compared the combination of carboplatin plus paclitaxel to carboplatin plus PDL in this clinical setting [5]. The study demonstrated improved progression-free survival in the PLD-containing arm (median: 11.3 months versus 9.4 months; hazard ratio: 0.82; $p=0.005$), and a quite surprising substantially lower risk of carboplatin-associated hypersensitivity reactions (grade ≥ 2 : 5% versus 18%). At the time of this preliminary report, data on overall survival were not available.

The somewhat unexpected results (both the improvement in progression-free survival and major reduction in hypersensitivity reactions) of this large phase 3 trial led us to re-examine, with longer follow-up, both the overall survival outcome and the incidence of allergic reactions in the previously reported SWOG carboplatin versus carboplatin plus PLD trial [4]. Reported here are the results of this analysis.

STUDY DESIGN

The details of this phase 3 trial have been previously presented [4]. In brief, patients entered into the study were required to have histologically-diagnosed stage III or IV cancer consistent with epithelial ovarian cancer, peritoneal carcinoma or mixed mullerian tumors and have relapsed within 6–24 months of the completion of their primary platinum-based chemotherapy program.

Patients were randomized to either receive intravenous single agent carboplatin (AUC 5) or carboplatin (AUC 5) plus PLD (30 mg/m²). Treatment on both study arms was repeated on an every 4-week schedule. Standard dose modifications were employed. Response and disease progression were defined according to standard RECIST criteria. Of note, the GCIG criteria for CA-125 progression were also utilized in this study [6].

STATISTICAL METHODS

The primary study endpoint was overall survival, and the accrual goal was 900 eligible patients. Due to an inadequate rate of accrual, the study was stopped by the SWOG Data and Safety Monitoring Committee when a total of 61 patients were registered, all of whom were eligible and evaluable [4].

Overall survival and progression-free survival estimates were calculated using the method of Kaplan-Meier (7), and 95% confidence intervals for their medians were constructed using the method of Brookmeyer-Crowley (8). Exact binomial confidence intervals were constructed for response and toxicity rates and comparisons were evaluated using a one-sided Fisher's exact test.

RESULTS

Details of the clinical characteristics of the patients entered into this phase 3 trial have been previously reported [4]. There were no major imbalances in known prognostic factors between the study arms. Thirty-one and 30 patients were treated with carboplatin plus PLD versus single agent carboplatin, respectively.

The confirmed complete and partial response rate in the combination chemotherapy regimen was 59% (16/27) [95% confidence interval: 39–78%], compared to 28% (8/29) in the single agent arm (95% confidence interval: 13–47%), [Fisher's exact $p=0.02$]. There were an additional 2 unconfirmed responders in each study arm.

All treated patients have now progressed or died (in contrast to 6 patients who were still alive and had not progressed at the time of the prior report). The estimated median progression-free survival was 12 months (95% confidence interval: 10–16 months) in the combination regimen, versus 8 months (95% confidence interval: 6–11 months) with single agent carboplatin ($p=0.02$) [Figure 1].

A total of 50 patients entered into this trial have now died (compared to 32 in the prior report). The estimated median overall survival is 31 months (95% confidence interval: 24–37 months) and 18 months (95% confidence interval: 15–29 months) for the combination and single agent therapy, respectively ($p=0.20$) [Figure 2].

There were no reports of hypersensitivity reactions in the carboplatin plus PLD arm (95% confidence interval: 0–11%), compared to 9 (30%) [95% confidence interval: 15–49%] patients treated with single agent carboplatin (Fisher's exact $p=0.0008$). Five (17% of patients) episodes were classified as being grade 3 or 4 in severity.

DISCUSSION

The re-analysis of survival observed in this prematurely terminated randomized trial in recurrent ovarian cancer, which attempted to compare single agent carboplatin to the combination of carboplatin plus PLD, has confirmed the earlier report of an improved time to disease progression associated with the two-drug strategy. These results are consistent with several other studies evaluating a platinum-based agent plus a second biologically active cytotoxic agent versus platinum alone in this setting [1,2].

However, with longer follow-up and more events, the provocative improvement in overall survival noted in the earlier report of this trial has not been sustained [4]. This outcome is almost certainly due to the favorable impact associated with the administration of an active agent *following the completion of treatment* on this protocol to patients initially managed on

the “inferior study arm” [9]. Of relevance to this conclusion, a similar discrepancy between an observed improvement in progression-free survival versus no impact on overall survival was noted in the phase 3 trial that compared carboplatin plus gemcitabine to single agent carboplatin [2]. Again, the positive effect of subsequent treatment in patients randomized to the carboplatin alone arm is the most likely explanation for this finding.

It is also important to acknowledge that due to the limited sample size in this randomized trial, statistical significance can be substantially influenced by changes in the outcome of only a few patients. Thus, in this setting it is reasonable to note the continuing differences between the median survivals of the two patient populations (31 months versus 18 months).

Of, perhaps, greatest interest was the rather striking difference in carboplatin-associated hypersensitivity reactions (0% versus 30%) noted in this small trial, a result that has now been confirmed in the much larger CALYPSO study [5]. The biological explanation for this observation is uncertain, but may relate to unique previously unrecognized short-term effects of liposomes on immune cells responsible for platinum allergic reactions. The enhancement of the opportunity to safely administer carboplatin [10,11], whose role is well-established in recurrent ovarian cancer, may be as relevant in this complex management scenario as the delivery of the second anti-neoplastic drug itself.

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Figure 1.
Progression-free survival by treatment arm

Figure 2.
Overall survival by treatment arm