Ovarian Cancer

MICHAEL V. SEIDEN

Division of Hematology and Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA

Key Words. Ovarian cancer · Treatment · ASCO

ABSTRACT

Ovarian cancer remains the most lethal gynecologic malignancy in women in the United States. Studies from this year’s American Society of Clinical Oncology more clearly defined the role of chemotherapy in women with early stage disease and now suggest that essentially all women with invasive disease should receive chemotherapy that contains carboplatin. Studies in women with advanced disease continue to support the use of carboplatin and paclitaxel in the treatment of women with newly diagnosed disease although early data suggest that carboplatin and docetaxel might be an acceptable alternative. Platinum-resistant disease remains a therapeutic challenge. Small molecules that inhibit the function of the epidermal growth factor receptor, such as OSI-774, and novel classes of chemotherapeutic agents, including the acylfulvene MGI-114 and epothilone B and its analogue, BMS247550, all warrant further study in this disease.

TREATMENT RECOMMENDATIONS FOR EARLY OVARIAN CARCINOMA

Can Patients with Relapsed Previously Untreated Stage I Epithelial Ovarian Cancer Be Salvaged? DF Kolomainen, R A’Hern, M Gore (ABSTRACT 803).

INTRODUCTION

The 37th annual meeting of the American Society of Clinical Oncology (ASCO) served to more clearly define treatment recommendations for women with early stage disease. Large studies evaluating the potential role and limitations of new two- and three-drug combinations in the treatment of women with chemotherapy-naïve ovarian cancer were also presented and generated extensive discussion at the meeting. In addition, the list of novel chemotherapeutic and biological agents that have activity in recurrent disease continue to expand. While the growing list of therapeutic agents provides fertile ground for future investigation, there were no dramatic discoveries in the treatment of either advanced or recurrent carcinoma.

TREATMENT RECOMMENDATIONS FOR EARLY OVARIAN CARCINOMA

Can Patients with Relapsed Previously Untreated Stage I Epithelial Ovarian Cancer Be Salvaged? DF Kolomainen, R A’Hern, M Gore (ABSTRACT 803).

RESULTS OF A RANDOMIZED TRIAL IN 923 PATIENTS WITH HIGH-RISK EARLY OVARIAN CANCER, COMPARING ADJUVANT CHEMOTHERAPY WITH NO FURTHER TREATMENT FOLLOWING SURGERY. IB Vergote, BJ Trimbos, D Guthrie, M Parmar, G Bolis, C Mangioni, A Anastasopolou, V Torri, J Vermorken (ABSTRACT 802).

The appropriate management of early stage ovarian carcinoma is controversial. In particular, there has been a long-standing debate as to which patients with early stage disease require therapy and what the exact magnitude of the benefit might be in this group of patients with a relatively good prognosis. Indeed, the relative infrequency of this patient population, coupled with variable staging and contamination of earlier studies with cases of borderline tumors, has made it difficult to perform well-powered studies with carefully defined patient populations.

This year, ASCO provides important information on the potential consequences of deferring therapy in patients with low-stage disease and provides information of the...
benefits of treating patients with adjuvant platinum-based chemotherapy after surgery. First, Drs. Kolomainen, A’Hern, and Gore reviewed their sizable experience with 194 stage I patients who were assigned to careful observation after resection of an apparently localized ovarian carcinoma. These patients were seen at The Royal Marsden Hospital, London, and were diagnosed between 1980 through 1994. The study is strengthened by the description of a carefully defined patient population and long follow-up but is challenged in that follow-up during the early time periods prior to the availability of computed axial tomography (CAT) scans or CA-125 [1]. Nevertheless, all the patients were followed on carefully defined protocols, which, in the early years, included ultrasound and even yearly laparoscopy. Specifically, the investigators reviewed their analysis of the 61 women (31% of the initial cohort) who developed recurrent carcinoma 1 to 16 years after primary surgery. Analysis of the initial cohort demonstrated that women with high-grade tumors, or higher stages (i.e., stage IC versus stage IA) were at slightly higher risk of recurrence while histology and the presence or absence of cyst rupture at initial surgery were not features that placed patients at higher risk for recurrence (Table 1).

At the time of recurrence, the majority of woman received single-agent carboplatin although many others received either cisplatin, platinum combination therapy, or in a few instances, alternative therapies. Defining the time of relapse as time zero, the median disease-free survival was only 1.8 years, and the overall median survival was 2.8 years from date of relapse. Women who relapsed and had clear cell histology or a prior history of cyst rupture had very dismal prognoses. Only 24% of women with tumor recurrence remained free of disease 5 years from the time of initial chemotherapy.

Disease-free survival curves have not yet plateaued, and with ongoing late relapses, it is likely that the very long-term salvage rate will be lower. Survival curves from the time of first recurrence for this patient population look similar to that of women with newly diagnosed stage III disease. In summary, these data demonstrate that recurrent ovarian cancer in a chemotherapy-naïve patient population is usually not curable. Subgroup analysis did not identify a subgroup of women with early stage disease that could be assured successful long-term salvage if initial therapy was deferred. Finally, women with recurrent clear cell carcinomas require a wider range of therapeutic options since it is unlikely that platinum-based therapies will provide long-term palliation.

Dr. Vergote presented on behalf of the International Collaboration on Ovarian Neoplasms (ICON) and Adjuvant Treatment in Ovarian Neoplasm (ACTION) investigators two prospective randomized trials of similar design that evaluated immediate therapy versus careful observation in woman with early stage ovarian cancer. Both trials included about 450 patients and had similar eligibility and treatment programs. Data were thus presented for the individual trials and pooled to provide greater power in defining the benefit of immediate therapy.

ICON I included women with early stage disease, while ACTION required somewhat more rigorously defined surgical staging and included women with stage IA or IB grade 2 or 3 tumors, all clear cell carcinomas, and all grade stage IC or II A tumors. The treatment arm was not defined but included platinum in essentially all women. Women receiving platinum-based adjuvant therapy had a longer disease-free and, most importantly, overall survival advantage, which reached a very high level of statistical significance. Specifically the hazard ratio was 0.64 (p = 0.001; confidence interval [CI] 0.5-0.83) and 0.68 (p = 0.01; CI 0.51-0.92) for disease-free survival and overall survival, respectively. The 5-year disease-free and overall survival rates were 76% and 82%, respectively, in the treated group and 65% and 75%, respectively, for the untreated group for an absolute disease-free survival benefit of 11% and survival benefit of 7% for women receiving immediate therapy.

Analysis of treatment recommendations varied between the trials and was predominantly single-agent carboplatin in the ICON I trial and combination-based cisplatin therapy in the ACTION trial. Reassuringly, each of the individual trials demonstrated the same findings with similar reductions in the risk of recurrence and death. Subgroup analysis performed in the ACTION trial suggested that therapy was most beneficial to the group of women who had less comprehensive staging at initial surgery and most likely a higher burden of occult residual tumor. While this evidence provides the strongest data to date that women with low-stage disease should receive chemotherapy, it still leaves unanswered two issues. First, is there any population of women with low-stage disease whose prognosis will not be improved by the delivery of chemotherapy? Second, in a group of women with only microscopic residual disease, why does therapy reduce the risk of death by only 33%?

THERAPY FOR NEWLY DIAGNOSED AND ADVANCED STAGE DISEASE

In the last few years, several groups have defined novel doublets and, in some cases, triplet regimens including carboplatin and, in the case of triplet regimens, carboplatin and paclitaxel. While these regimens have demonstrated impressive response rates in well-conducted phase II trials, none had been compared in a large randomized trial to the now-standard paclitaxel and carboplatin regimen. This year’s ASCO presented two important studies, both containing over 1,000 patients, comparing the standard paclitaxel and carboplatin...
regimen to either docetaxel with carboplatin [2,3] or, alternatively, the triplet carboplatin, epirubicin, and paclitaxel [4].

Preliminary Results of the SCOTROC Trial: a Phase III Comparison of Paclitaxel-Carboplatin (PC) and Docetaxel-Carboplatin (DC) as First-Line Chemotherapy for Stage IC-IV Epithelial Ovarian Cancer. P Vasey on behalf of the Scottish Gynecologic Cancer Trials Group (ABSTRACT 804).

The Scottish Randomized Trial in Ovarian Cancer (SCOTROC) investigators designed a trial that built on their previous phase II experience with docetaxel and carboplatin [2]. The current phase III trial compared 3-hour paclitaxel at 175 mg/m² with carboplatin to docetaxel at 75 mg/m² over 1 hour and carboplatin. Platinum dosing (area under the curve [AUC] = 5), schedule, and cycle length were identical in the two treatment arms. As with other studies done by this group, the patients were somewhat heterogeneous in terms of stage and degree of surgical cytoreduction although 80% of patients were International Federation of Gynecology and Obstetrics (FIGO) stage III/IV and two-thirds were optimally cytoreduced. Both regimens were deliverable at full doses in the majority of patients although there was increased patient withdrawal in the paclitaxel arm for cumulative neurotoxicity and a modest increase in patient withdrawal in the docetaxel arm for hypersensitivity reactions.

Careful review of neurotoxicity and accompanying quality-of-life questionnaires suggested that neuropathy was troublesome to many of the women on the paclitaxel arm, with 30% of women having greater than grade 1 sensory neuropathy. Growth factor requirements and hospitalization for fever and neutropenia were significantly higher in the docetaxel arm (Table 2). Complete response rates and overall response rates were equivalent in the trial (Table 3). Survival data are still immature with only 8 months of median follow-up, but to date, overall survival for the two groups appears equivalent. Further follow-up of the two treatment arms will be required to determine if efficacy differences become apparent with time. If survival proves to be equivalent, it will provide an alternative treatment strategy for this patient population which might have advantages in women with newly diagnosed advanced disease who have underlying neuropathic conditions.


The second large randomized trial addressed the potential efficacy of a three-drug regimen as compared to the standard two-drug regimen and, specifically, the value of adding an anthracycline to the taxane/platinum doublet [4, 5]. The trial built on the investigators’ phase II experience [4] and was well designed with randomization generating
well-balanced strata in this very large study. Importantly, epirubicin was added to the platinum/taxane doublet without altering the dose or schedule of the two standard drugs. Twelve hundred women were enrolled, and median follow-up is now 2.5 years. The incidence of grade III or IV toxicity was significantly higher in the triplet regimen. Complete response rates, overall response rates, and progression-free survival were not statistically different. Overall survival for the subgroup of women with suboptimal surgical cytoreduction at initial debulking was also equivalent. There are still not enough events (i.e., deaths) in the optimally cytoreduced arm to make definitive conclusions; however, at this point, the platinum/paclitaxel regimen remains the preferred choice due to apparent clinical equivalence and superior toxicity profile of the two-drug regimen.

Further information on the potential role of triplets or sequential doublets will await the mature data from this trial as well as other very large randomized trials. In particular, the Gynecologic Oncology Group (GOG) 182, a trial comparing two different sequential doublet regimens and two different triplet regimens to eight cycles of paclitaxel and carboplatin, will provide important data as to the potential role of alternative multidrug therapies in the treatment of this disease.

**RECURRENT EPITHELIAL OVARIAN CANCER**

**Carboplatin and Paclitaxel as Initial Second-Line Therapy in Recurrent Epithelial Ovarian Carcinoma.**

_D Dizon, M Hensley, P Sabbatine, E Poynor, A Hummer, E Venkatraman, D Spriggs (ABSTRACT 809)._  

The optimal management of recurrent ovarian carcinoma remains unclear, and indeed, the number of potential therapeutic options continues to grow although strategies for the most appropriate treatment for various clinical scenarios remain undetermined. Dr. Spriggs and colleagues retrospectively reviewed the Memorial Sloan-Kettering Cancer Center experience with the retreatment of chemosensitive patients with a first recurrence of their ovarian cancer with paclitaxel and carboplatin. The specific cohort of women selected for review was 84 women who had achieved clinical complete responses to their first treatment with carboplatin and paclitaxel and all were potentially platinum sensitive with ≥6 months from the conclusion of their primary therapy. Twenty of the women were surgically cytoreduced at the time of recurrence, with 17 women undergoing “complete” cytoreduction. This group did very well with retreatment, with 68% of women achieving a response including a complete response rate of 42%. Three-year survival, measured from the time of retreatment, was 72% and correlated with the length of first remission, as shown in Table 4.

**Phase III Randomized Trial of High-Dose Chemotherapy and Peripheral Blood Stem Cell Support as a Consolidation in Patients with Responsive Low-Burden Advanced Ovarian Cancer: Preliminary Results of a GINECO/FNCLCC/SGFM-TC Study.**

_H Curé, C Battista, JP Gusastall, M Fabbro, N Tubiana-Mathieu, H Bourgeois, B Lioure, C Homme, B Chiurazzi, D Paraïso, E Pujadé-Lauraine (ABSTRACT 815)._  

Recent analysis of the International Bone Marrow Transplant Registry demonstrates that high-dose therapy with autologous stem cell transplant can result in a portion of women surviving free of disease recurrence for several years, but whether this represents an improvement in therapy versus careful selection of drug-sensitive patients is unclear [6]. French investigators presented preliminary data from a randomized trial evaluating the efficacy of high-dose carboplatin (total dose, 1,600 mg/m²) and cytoxan (total dose, 6,000 mg/m²) versus three additional cycles of standard dose cytoxan and carboplatin in a carefully defined collection of women with stage III/IV ovarian cancer. Specifically, women younger than 60 years who had an objective response to front-line platinum therapy as determined by second-look laparotomy were then immediately randomized to receive either high-dose therapy with autologous peripheral stem cell rescue with filgrastim support versus three additional cycles of carboplatin (300 mg/m²) and cyclophosphamide (600 mg/m²) delivered on a 28-day schedule.

The study included 110 young women with small-volume disease immediately after 4-6 cycles of carboplatin-based therapy. Patients were randomized 1:1 between the two treatment arms although 10 of 55 women randomized to the high-dose therapy did not undergo planned therapy. Median hospitalization on the high-dose arm was 21 days, with 2 toxic deaths as well as a 15% rate of grade 4 mucositis. Median disease-free survival (from inclusion on study) was 11 months on the standard arm and 22 months on the high-dose arm. Follow-up is still limited, and an overall survival advantage has not emerged in either arm.

### Table 4. Overall survival for women retreated with carboplatin and paclitaxel

<table>
<thead>
<tr>
<th>Initial treatment-free interval</th>
<th>3-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 months</td>
<td>49</td>
</tr>
<tr>
<td>12-24 months</td>
<td>63</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>84</td>
</tr>
</tbody>
</table>
Multivariate analysis suggests that high-dose therapy is an independent variable for predicting disease-free survival. While the results are intriguing, it is unclear if the study will be large enough to demonstrate meaningful survival differences. In addition, physician, patient, and insurance biases might make it impossible to perform a confirmatory trial in the event the trial demonstrates a modest survival benefit. At this time, the use of high-dose therapy with autologous stem cell rescue remains investigational.

TREATMENT STRATEGIES FOR PLATINUM-RESISTANT DISEASE

There were few new insights into the appropriate management of platinum-/taxane-resistant disease presented at ASCO this year. While several presenters provided data to support the modest activity of gemcitabine, topotecan, oxaliplatin, etoposide, and irinotecan in platinum-resistant disease, there was no emerging information to suggest that any of these therapies possessed robust or durable clinical activity for the majority of these patients. A few novel agents were presented that will warrant further study in this difficult-to-treat patient population.


Normal and aberrant members of the epidermal growth factor receptor (EGFR) family have been identified on the surface of a subset of ovarian cancers. The prognostic and biologic significance of these receptors remains incompletely defined, yet laboratory experiments manipulating signaling through these receptors can retard tumor growth in some experimental systems [6-8]. OSI-774 is a small molecule that inhibits the tyrosine kinase activity of the EGFR, a molecule frequently overexpressed on ovarian tumors. This molecule, or other members of the class, has demonstrated activity in lung cancer, colon cancer, and head and neck tumors. In this phase II study, patients were treated daily with oral OSI-774. Thirty-four women, all with EGFR-overexpressing tumors, were assigned to treatment with 150 mg OSI-774 by daily oral dosing. There were three documented partial responses, and 42% of women had stable disease (defined as greater than 3 months of disease stability). Toxicity was consistent with other molecules in the class and included dermatitis (31 of 34 patients) and less often diarrhea. In no case did drug toxicity lead to patient withdrawal from therapy. In summary, this agent demonstrates an acceptable safety profile during at least moderately long-term administration. Documented responses along with a high rate of stable disease identify this drug as worthy of further study. The value of this agent in the treatment of ovarian cancer will require randomized trials either after or with conventional chemotherapy.


Sarosy, Reed, and colleagues updated their experience with MGI-114 (6-hydroxymethylacylfulvene; irofulven), the first of the acylfulvenes to enter clinical trial [9]. This acylfulvene, isolated from the Jack-O-Lantern mushroom (Omphalotus olearius), has broad tumoricidal activity through an unclear molecular mechanism, including inhibition of DNA, RNA, and protein synthesis. Other activities, including telomerase inhibition have also been described [10]. In this phase II study, a heterogeneous collection of women with both potentially platinum-sensitive and platinum-resistant disease received 4 consecutive days of MGI-114 at 11 mg/m² on a 28-day cycle [9]. The drug was associated with moderate gastrointestinal toxicity, moderate or marked fatigue, and myelosuppression. Thrombocytopenia was cumulative with cycles and occasionally of prolonged duration. Loratidine was effective at reducing fatigue. One complete response, five partial responses, and seven stable responses were seen in 27 women. Two responses of more than 1 year of duration were seen in women with platinum-resistant disease. While this drug is clearly active in recurrent ovarian cancer, toxicity issues have lead to the development of alternative schedules, which are currently being used in a recently opened phase II clinical trial [11].


Epothilone A and B are natural marine products and BMS-247550 is an Epothilone B analogue [12, 13]. All three molecules demonstrate broad antitumor activity, bind tubulin, and demonstrate activity in taxane-resistant tumors in vitro.
They also demonstrate activity in tumor cell lines that overexpress the transmembrane drug export protein MDR-1, suggesting that the epothilones are not substrates for MDR-1. Drs. Mani and Rubin presented phase I trials, reviewing the safety, maximum tolerated dose, and preliminary clinical activity of these molecules. Dose-limiting toxicity with the current schedules was diarrhea. Responses were seen in both trials in women with taxane-treated ovarian cancer. Phase II trials in ovarian carcinoma are under way with both of these interesting compounds.

REFERENCES


