Challenges for chemotherapy in ovarian cancer

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Background: Ovarian cancer is treated with surgery followed by combination chemotherapy with paclitaxel plus carboplatin. In an effort to improve outcomes, clinical trials are evaluating the following strategies: maintenance therapy; intraperitoneal drug administration; new combinations; novel cytotoxics; combination chemotherapy for recurrent disease; and molecular-targeted therapies.

Patients and methods: Clinical trials evaluating the above strategies are being performed in ovarian cancer in patients with: (1) previously untreated advanced ovarian cancer; (2) platinum-sensitive recurrent disease; and (3) platinum-resistant recurrent disease.

Results: Combination chemotherapy regimens are superior to single-agent therapy in recurrent ovarian cancer. Molecular-targeted therapy has produced objective responses in previously treated patients. Maintenance therapy of any type has not been shown to prolong survival. Intraperitoneal therapy has resulted in improved survival with considerable toxicity in patients with small-volume stage III disease.

Conclusions: Numerous novel clinical strategies are being evaluated in ovarian cancers that have the potential to improve outcomes compared to standard therapy.

Key words: combination chemotherapy, intraperitoneal therapy, maintenance therapy, novel agents, ovarian cancer, targeted therapy

Introduction

Ovarian cancer remains the most lethal gynaecologic cancer in the western world. Worldwide there will be almost 200 000 cases diagnosed per year and approximately 115 000 deaths. The major reason for the high morbidity associated with the diagnosis of epithelial ovarian cancer is primarily due to the fact that at least 75% of patients are diagnosed with metastatic advanced disease (FIGO stages III and IV). While surgery is an important component of initial therapy, most patients cannot be cured by surgery alone due to residual microscopic and macroscopic peritoneal implants. Ovarian cancer is a chemosensitive disease and numerous chemotherapeutic agents have been shown to produce objective responses following surgery. Current treatment with combination chemotherapy results in a clinical complete remission rate in approximately 75% of all patients with advanced ovarian cancer. However, median progression-free survival ranges from 16 to 21 months, depending upon the volume of disease at the time chemotherapy was initiated [1]. Median overall survival ranges from 24 to 60 months and is dependent also on the volume of disease at diagnosis. Median survival following relapse from initial therapy is approximately two years. Consequently, while overall survival has been minimally improved with modern chemotherapy, there has been a significant improvement in five-year survival rates, which have increased from 30% in the 1960s to almost 50% in the current decade [2].

Current chemotherapy

The two-drug combination of carboplatin plus paclitaxel is the current standard regimen for advanced ovarian cancer. Carboplatin/paclitaxel has been compared to cisplatin/paclitaxel (the previous standard regimen) [3, 4] in two large prospective randomized trials. The Gynecologic Oncology Group (GOG) performed a non-inferiority study comparing cisplatin/paclitaxel versus carboplatin/paclitaxel in optimally debulked (no tumor nodule greater than 1 mm after initial surgery) stage III patients [5]. The standard therapy consisted of cisplatin (75 mg/m²) and paclitaxel (135 mg/m² in a 24-h infusion) every two weeks for a total of six cycles. In the experimental arm, carboplatin was dosed to an AUC of 7.5 combined with paclitaxel (175 mg/m² in a 3-h infusion). Median progression-free survival and overall survival were 19.4 and 48.7 months, respectively, for patients treated with cisplatin/paclitaxel compared to 20.7 and 57.4 months for the carboplatin/paclitaxel-treated patients. The relative risk (R.R.) of progression for the carboplatin/paclitaxel group was 0.88 (95% C.I., 0.75–1.03) and the R.R. of death was 0.84 (95% C.I., 0.7–1.02). Overall, the carboplatin/paclitaxel-treated group of patients experienced less toxicity, and it was concluded that carboplatin/paclitaxel was less toxic, easier to administer, and not inferior when compared to cisplatin/paclitaxel.

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times were also not statistically different, 43.3 months versus 44.1 months. Mean global quality of life scores were statistically significantly better in the carboplatin/paclitaxel-treated patients. These two studies established carboplatin/paclitaxel as the standard of care for patients with advanced ovarian cancer.

In the GOG trial, 90% of patients were in a clinical complete remission following six cycles of carboplatin/paclitaxel with normal CA-125 levels and no evidence of ovarian cancer on physical examination or by imaging studies. Unfortunately, most patients with ovarian cancer recur. Median survival for patients following recurrence in the GOG study was approximately two years, and all patients with recurrent ovarian cancer will ultimately succumb to their disease.

Carboplatin/paclitaxel is a generally well-tolerated regimen. However, toxicities can be significant and include myelosuppression, neuropathy, and alopecia. While carboplatin/paclitaxel represents an improvement in care for patients with advanced ovarian cancer, most patients still die from their disease. It is clear that the challenge for chemotherapy in ovarian cancer is to develop more effective regimens that have less toxicity, both for induction chemotherapy and for patients at the time of relapse. Table 1 summarizes strategies that are currently being evaluated in clinical trials to improve treatment outcomes in ovarian cancer.

**maintenance therapy**

Since most patients with ovarian cancer who obtain a clinical complete remission following induction chemotherapy will ultimately relapse, numerous strategies have been tested in an effort to prevent or delay recurrences. There currently is no evidence that any form of maintenance therapy improves survival in patients who achieve a clinical complete remission following initial therapy [7]. Several trials have evaluated the impact of maintenance chemotherapy in this clinical situation. A GOG trial randomized patients to three versus 12 cycles of monthly paclitaxel (175 mg/m² in a 3-h infusion) [8]. This study was closed after a scheduled interim analysis demonstrated that patients who received the 12 cycles of maintenance therapy had a statistically significant improvement in progression-free survival (28 months vs. 21 months). Due to the early closure of this study, and to the fact that patients randomized to the three cycles of chemotherapy were given the option to receive an additional nine cycles of chemotherapy, survival cannot be evaluated in this trial. Maintenance paclitaxel was also associated with significant toxicity, particularly neurotoxicity. Consequently, the GOG will be performing another randomized trial in this group of patients in which survival will be the endpoint. Patients who achieve a clinical complete remission will be randomized to receive no further therapy, treatment with 12 months of maintenance paclitaxel, or treatment with a novel pegylated paclitaxel compound [9]. In addition, an Italian study is also randomizing patients to either observation or weekly paclitaxel [10]. Previous studies, however, have failed to show that additional therapy with topotecan [11, 12] or epirubicin [13] improves survival in patients who achieved a complete remission. Furthermore, a recent study of high-dose consolidation therapy, which required autologous stem cell transplantation, also reported a lack of survival benefit compared to treatment with standard doses of chemotherapy [14]. Immunotherapy with gamma interferon [15] or yttrium-90-labeled HFMG1 [16] administered intraperitoneally has failed to impact upon survival. A randomized controlled trial of an antibody against CA-125 versus placebo is currently in progress in a select group of patients who achieve a clinical complete remission following induction therapy [17]. Maintenance intraperitoneal cisplatin has also been studied in a prospective randomized trial compared to observation in patients who achieved a complete remission following intravenous cisplatin-based therapy [18]. While there was a suggestion of a treatment effect, there was no statistically significant improvement in survival.

**intraperitoneal drug delivery**

Intraperitoneal (IP) chemotherapy has been studied for over two decades in patients with small-volume ovarian cancer. The primary rationale for IP chemotherapy is the fact that ovarian cancer remains primarily an intraperitoneal disease and that administration of drugs directly into the peritoneal cavity will lead to a pharmacologic advantage resulting in higher intratumoral drug concentrations as compared to intravenous administration [19]. Three large prospective randomized trials have been conducted in the United States [20–22] and the results are summarized in Table 2. All three studies have produced an improvement in survival for patients treated on the IP arm. However, IP therapy has not been generally accepted as standard therapy for ovarian cancer patients because of the excessive toxicity associated with IP therapy [19]. Furthermore, other factors may have accounted for the improved results observed with the patients randomized to the IP arm, such as length of treatment and differences in dose intensity. The GOG plans to perform additional phase II trials to determine whether less toxic IP regimens can be developed.

<table>
<thead>
<tr>
<th>Table 1. Potential new treatment approaches in ovarian cancer</th>
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<tbody>
<tr>
<td>Maintenance therapy in patients who achieve a complete remission with standard therapy: cytotoxic chemotherapy or biological agents</td>
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<tr>
<td>Intraperitoneal chemotherapy instead of intravenous administration</td>
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<tr>
<td>New combination chemotherapy regimens instead of carboplatin/paclitaxel</td>
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<td>More effective treatment for recurrent disease after initial chemotherapy</td>
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<tr>
<td>Molecular-targeted therapies</td>
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<tr>
<td>Development of novel cytotoxic agents</td>
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Numerous drugs have been shown to have activity as second-line agents in patients who receive initial treatment with carboplatin/paclitaxel. A series of prospective randomized trials are in progress evaluating novel combinations, comparing them to standard therapy with carboplatin/paclitaxel (Table 3). In three of the studies, the experimental arm has replaced paclitaxel with another agent, such as docetaxel [23], gemcitabine [24], or liposomal doxorubicin [25]. The results of the study in which paclitaxel has been replaced by docetaxel have been reported while the other two studies are still ongoing [23]. The carboplatin/docetaxel combination appears to have equivalent activity but a different spectrum of toxicity compared to carboplatin/paclitaxel. Epirubicin [26, 27], gemcitabine [28, 29], topotecan [30], and liposomal doxorubicin [31] have also been evaluated in combination with carboplatin/paclitaxel, either in the form of triplets or in sequential doublets. Initial results indicate that the addition of epirubicin has failed to impact upon survival [27]. The schema for the largest study of novel combinations in ovarian cancer is shown in Figure 1 [31]. This study has accrued over 4000 patients and preliminary results are expected in 2006.

**novel cytotoxics**

As noted, a major goal is to develop more effective chemotherapy regimens for ovarian cancer. A series of agents are being studied with novel mechanisms of action in previously treated patients with ovarian cancer with the ultimate goal of incorporating these drugs in the initial therapy of patients with advanced disease. Table 4 summarizes some of the new agents currently under evaluation, their mechanisms of action, and preliminary results.

**treatment of recurrent disease**

Another major challenge for chemotherapy in ovarian cancer is to develop more effective regimens for treatment of patients with recurrent ovarian cancer. The primary goal of therapy in these patients is management of symptoms since a cure is essentially not feasible. Several factors [36] have been identified to be predictors of response to chemotherapy in patients with recurrent ovarian cancer, including histology, tumor size, and the disease-free interval. Patients have traditionally been categorized as having platinum-sensitive disease if the disease-free interval is greater than 6 months [37]. Until recently, treatment with single-agent carboplatin has been the standard regimen for patients with platinum-sensitive recurrent ovarian cancer [38]. More recently, two large trials have demonstrated that combination chemotherapy is more effective than single-agent carboplatin in this situation.

The ICON4/AGO/OVAR 2.2 trial was an international multicenter randomized trial in 802 patients with platinum-sensitive ovarian cancer [39]. Patients in this study were randomly assigned to treatment paclitaxel plus platinum (in most cases, carboplatin) or conventional platinum-based therapy (in most cases, single-agent carboplatin). With
A PHASE III RANDOMIZED TRIAL OF PACLITAXEL AND CARBOPLATIN VERSUS TRIPLET OR SEQUENTIAL DOUBLET COMBINATIONS IN PATIENTS WITH EPITHELIAL OVARIAN OR PRIMARY PERITONEAL CARCINOMA

ELIGIBILITY
• Epithelial ovarian or primary peritoneal cancer
• FIGO Stage III-IV, optimal and suboptimal

STRATIFICATION
• No gross residual disease
• vs macroscopic residual disease
• vs macroscopic residual disease with intent to perform interval cytoreduction

RANDOMIZATION
• All Patients
• Equal proportions on each regimen
• Primary Endpoints:
  - Progression-Free Survival (PFS)
  - Overall Survival (OS)
  - Response Rate (RR)

MONITORING AND INTERVENTIONS
• Patients in Clinical Complete Remission:
  - No second-look surgical procedures
  - No post-remission therapy
• Patients with Gross Residual Disease:
  - Optional interval cytoreduction after cycle 4
  - Monitor Clinical and Biological Disease Status

Table 4. Novel cytotoxics in ovarian cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reference</th>
<th>Mechanism of action</th>
<th>Status</th>
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<tbody>
<tr>
<td>Epothilone</td>
<td>[32]</td>
<td>Tubulin inhibitor distinct from taxanes</td>
<td>Phase II trials in progress</td>
</tr>
<tr>
<td>TLK286</td>
<td>[33]</td>
<td>Glutathione prodrug activated by GSTp</td>
<td>15% response rate in phase II trial. Current trials comparing it with topotecan or liposomal doxorubicin in progress.</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>[34]</td>
<td>Multitargeted antifolate</td>
<td>Phase II trials in progress</td>
</tr>
<tr>
<td>Yondelis</td>
<td>[35]</td>
<td>Binds to minor groove in DNA</td>
<td>Active as single agent (26% response rate). Study ongoing in combination with liposomal doxorubicin.</td>
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Table 6 summarizes the results of this trial and compares them to the trial of paclitaxel plus platinum versus platinum in a similar group of patients. The overall response rate for the combination of carboplatin/gemcitabine was significantly higher for the single-agent carboplatin (47.2% vs. 30.9%).

The AGO group [40] performed another phase III trial in which 356 patients with platinum-sensitive disease who were randomized to receive either single-agent carboplatin (AUC = 5) or the combination of gemcitabine (1000 mg/m² day 1, day 8) together with carboplatin (AUC = 4) on day 1. The AGO trial was not powered to detect the differences in overall survival.

Figure 1. GOG 182 schema
There were significant differences in toxicity between paclitaxel/carboplatin and gemcitabine/carboplatin in this group of patients with platinum-sensitive recurrent ovarian cancer. Paclitaxel/carboplatin has increased neurotoxicity and alopecia compared to carboplatin/gemcitabine. Carboplatin/gemcitabine appears to have increased myelotoxicity compared to paclitaxel/carboplatin, but the consequences of myelosuppression, such as infection, are not significantly different between the two treatments. Which particular combination to use for an individual patient with platinum-sensitive recurrent ovarian cancer will primarily depend upon toxicity considerations as well as patient preference. Additional combinations of cytotoxic agents and targeted therapies will be evaluated in recurrent ovarian cancer to determine if even greater improvements in progression-free and overall survival are possible.

**biological therapies**

Numerous agents are currently under development that are aimed at molecular targets in a variety of malignancies. These compounds are also being investigated in ovarian cancer. In particular, inhibition of epidermal growth factor receptor (EGFR) and vascular epithelial growth factor (VEGF) have been studied in clinical trials, both as single agents and in combination with chemotherapy. Gefitinib and erlotinib are small molecules that inhibit the enzyme activity of the EGFR receptor tyrosine kinase. In ovarian cancer, erlotinib [41] produced a response rate of 8.8% as a single agent for heavily pretreated patients (median, three prior regimens) whereas gefitinib [42] induced a single response in long-term stable disease in three additional patients and 27 patients with recurrent ovarian cancer. Cetuximab, an anti-EGFR monoclonal antibody, has been shown to improve response rate and time to progression for patients with metastatic colorectal cancer in combination with irinotecan [43]. Cetuximab is currently undergoing evaluation as a single agent in patients with recurrent ovarian cancer [44]. It also has been evaluated in combination with paclitaxel/carboplatin in previously untreated patients with advanced ovarian cancer. In this pilot study, there was a high complete response rate (87%). It was also shown that maintenance cetuximab was feasible [45].

It is likely that the next generation of EGFR inhibitors will affect the interactions of erb-B family members. Lapatinib blocks the activity of the tyrosine kinases of both EGFR (erbB1) and HER2 (erbB2) [46]. Clinical trials of this agent will be initiated in ovarian cancer. The antibody pertuzimab (2C4) binds to the dimerization site of HER2, inhibiting its interaction with the other members of the erbB family. Responses have been reported with this agent in patients with recurrent ovarian cancer [47]. Trials are in progress evaluating pertuzimab in combination with chemotherapy (gemcitabine).

The GOG [48] recently reported the results of a clinical trial of bevacizumab, the antibody targeting VEGF. This agent demonstrated significant activity as a single agent in patients with recurrent ovarian cancer (17% response rate). In addition, bevacizumab has been shown to improve survival when combined with chemotherapy in patients with breast [49], lung [50], and colorectal cancer [51]. Consequently, the GOG is performing a prospective randomized trial in previously untreated patients as outlined in Figure 2. This will be the first randomized trial in ovarian cancer evaluating whether combination chemotherapy with paclitaxel/carboplatin can be enhanced by the addition of bevacizumab and whether bevacizumab maintenance therapy is beneficial. Table 5 summarizes various molecular-targeted therapies that are being evaluated by the GOG and the results of preliminary studies of novel combinations of targeted therapies and chemotherapy. In addition to cetuximab and bevacizumab, which are being evaluated in combination with chemotherapy, there have been preliminary studies of bortezomib, gefitinib, and erlotinib in combination with chemotherapy. These trials have suggested that combinations of chemotherapy with molecular-targeted agents are feasible. The major challenge for chemotherapy in
**Table 5. Molecular-targeted therapies and combination trials**

<table>
<thead>
<tr>
<th>Single agents (recurrent disease)</th>
<th>Proteosome Inhibitor</th>
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<tbody>
<tr>
<td>Bortezomib</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>Bryostatin</td>
<td>Protein Kinase C Inhibitor</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2 Inhibitor</td>
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<tr>
<td>R11577</td>
<td>Farnesyltransferase Inhibitor</td>
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<tr>
<td>BAY 43–0006</td>
<td>RAF-1 Kinase Inhibitor</td>
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**Combinations of molecular-targeted therapy and chemotherapy**

<table>
<thead>
<tr>
<th>Carboplatin + Docetaxel plus Erlotinib</th>
<th>Carboplatin plus Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine; Osalplatin plus Gefitinib</td>
<td>Carboplatin plus Bortezomib</td>
</tr>
<tr>
<td>Carboplatin + paclitaxel + Cetuximab</td>
<td>Carboplatin + Paclitaxel + Bevacizumab</td>
</tr>
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**disclosures**

Dr Ozols has indicated that he is a member of advisory boards and/or a consultant for Bristol-Myers Squibb, Lilly, Tibotec, United Therapeutics and Genentech.

**references**


24. Randomized comparison of gemcitabine plus paclitaxel versus paclitaxel plus carboplatin in previously untreated ovarian cancer. Eli Lilly Trial, in progress.


34. Gynecologic Oncology Group phase II trial in progress.


44. Schiller RJ. Phase II trial of cetuximab in recurrent ovarian cancer. Trial in progress.


47. Gordon MS, Matei D, Aghajanian C et al. Clinical activity of pertuzumab (huMab 2C4) in advanced, refractory or recurrent ovarian cancer (OC), and the role of HER2 activation status. Proc Am Soc Clin Oncol 2005; 24: 467s (Abstr 5051).


