New, Expanded, and Modified Use of Approved Antineoplastic Agents in Ovarian Cancer

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Key Words. Ovarian cancer • Cancer chemotherapy • Combination chemotherapy • Second-line chemotherapy

ABSTRACT

Over the past several years, clinical research efforts in ovarian cancer employing a number of U.S. Food and Drug Administration (FDA)-approved antineoplastic agents have permitted the development of approaches that both improve the effectiveness and decrease the toxicities of systemic therapy of ovarian cancer. These initiatives, including prospective trials and retrospective examinations of large clinical experience, have involved agents previously approved by the FDA for use in ovarian cancer (e.g., cisplatin, paclitaxel, topotecan, and liposomal doxorubicin) and the development of new strategies for drugs approved for other malignant conditions (e.g., gemcitabine, docetaxel, etoposide, irinotecan, vinorelbine, and bevacizumab). It can be anticipated that future studies involving novel approved agents will further expand the oncologist’s weapons against ovarian cancer. The Oncologist 2007; 12:186–190

INTRODUCTION

Over the past several decades, trials in ovarian cancer have resulted in initial approval of a number of novel antineoplastic agents by the U.S. Food and Drug Administration (FDA), with subsequent studies in other tumor types substantially expanding the indications for their routine clinical use. For example, both carboplatin and paclitaxel, two of the most frequently employed agents in oncologic practice, were first examined for their clinical utility in women with ovarian cancer [1–3].

Recently, however, this drug development paradigm has reversed course. Chemotherapy agents active in other tumor types have subsequently been explored in patients with ovarian cancer, with positive results. Furthermore, during the last few years, considerable clinical research efforts in this area have focused on optimizing the benefits associated with drugs already known to be active in the malignancy. This review highlights important recently reported ovarian cancer studies involving FDA-approved antineoplastic agents and their impact on routine management of the malignancy.

PACLITAXEL

Despite the long-established role of paclitaxel in ovarian cancer [3, 4] and extensive trial experience with the drug in the disease, recently reported data have clearly demonstrated that there is much more to learn regarding this important antineoplastic drug to further optimize its use in the treatment of this female pelvic cancer [5–8].

Several multicenter phase II trials have revealed that weekly administration of paclitaxel results in a 20% objective response rate in ovarian cancer patients with clinically defined platinum- and paclitaxel-resistant (“standard” 3-week schedule) disease [5, 6]. (Note that the definition of both platinum- and paclitaxel-resistant ovarian cancer is...
failure to respond to prior platinum and paclitaxel treatment or documented disease recurrence within 6 months of the completion of such therapy.)

The biological explanation of this provocative observation is uncertain but may relate to the recognized cell-cycle specificity of paclitaxel cytotoxicity. Alternatively, the documented tumor shrinkage could be related to an entirely different mechanism of action (e.g., antiangiogenesis).

A phase III trial underway in Japan compares carboplatin plus standard paclitaxel (3-week schedule) to a program of carboplatin plus weekly paclitaxel employed as primary treatment of advanced ovarian cancer and has recently competed accrual. The results of this study, which should be available within the next 2 years, hold considerable interest.

For the present, based on existing data, it is appropriate to conclude that the weekly delivery of paclitaxel is an acceptable treatment option for patients with resistant (both platinum and every 3-weeks paclitaxel) ovarian cancer [5, 6].

In the setting of recurrent disease, where patients had a treatment-free interval of at least 6 months, paclitaxel plus a platinum agent were directly compared to a platinum agent without paclitaxel in a randomized phase III trial [9]. This somewhat complex study (International Collaborators in Ovarian Neoplasm [ICON]-4) revealed that the two-drug combination containing paclitaxel was associated with both longer progression-free and overall survival (2-year survival, 57% vs. 50%; \( p = .02 \)) compared with the nonpaclitaxel-containing program [9]. Because most patients treated with paclitaxel received carboplatin as the platinum agent, and the control arm was most commonly single-agent carboplatin, most oncologists have interpreted this study to demonstrate the superiority of second-line carboplatin plus paclitaxel compared with carboplatin alone in the setting of recurrent ovarian cancer.

Unfortunately, the combination regimen was also associated with a far greater risk of clinically relevant neuropathy (grade 2–3, 20% vs. 1%) [9]. However, for a patient who has not experienced significant neurotoxic effects from her prior primary platinum/taxane regimen, this two-drug combination is a rational approach in the setting of recurrent disease.

**Docetaxel**

A phase III randomized trial has demonstrated the therapeutic equivalence of carboplatin plus docetaxel, compared with carboplatin plus paclitaxel, when employed as primary treatment of advanced ovarian cancer [10]. The regimens differ in their toxicity profiles, with the paclitaxel-containing program being associated with a higher incidence of peripheral neuropathy and the docetaxel program having a greater risk of clinically relevant neutropenia. The data clearly demonstrate that either carboplatin-based combination may be employed as primary therapy of advanced ovarian cancer.

It should also be noted that previously reported phase II trial data had revealed that the use of single-agent docetaxel resulted in an objective response rate of approximately 20% in patients with platinum- and paclitaxel-resistant (3-week schedule) ovarian cancer [11, 12]. Thus, this drug is another rational management option in the setting of resistant disease.

**Cisplatin**

Although cisplatin is a very well-established agent in the treatment of ovarian cancer, the results of three randomized phase III trials revealing that the intraperitoneal delivery of the drug resulted in a 20%–25% improvement in the risk of death compared with intravenous administration led the National Cancer Institute to issue a “Clinical Announcement” informing oncologists, patients, and the public of this outcome in early 2006 [8, 13, 14]. Future studies in this arena will hopefully seek to optimize use of this drug-delivery technique, employing both cisplatin and other antineoplastic agents (e.g., carboplatin and paclitaxel).

**Gemcitabine**

Phase II trial data have shown that gemcitabine produces objective responses in approximately 10%–15% of patients with platinum-resistant ovarian cancer, making this a reasonable therapeutic option in this clinical setting [15, 16].

A recently reported phase III trial examined the clinical utility associated with a combination carboplatin-plus-gemcitabine regimen compared with single-agent carboplatin in women with recurrent ovarian cancer [17]. The treated population was similar to that evaluated in the previously noted ICON-4 study. The trial results revealed that the combination program produced a higher objective response rate and longer progression-free survival compared with the single-agent regimen. However, there was no difference in overall survival found between the study arms.

Of note, in contrast to the ICON-4 results, the incidence of peripheral neuropathy was the same for single-agent carboplatin and the combination strategy. Thus, despite the lack of impact on overall survival associated with the carboplatin-plus-gemcitabine regimen, this combination chemotherapy approach is a highly reasonable option for patients with recurrent ovarian cancer where there is concern for the potential toxicity (risk of neuropathy) of a carboplatin-plus-paclitaxel program.

**Topotecan**

Topotecan is well established as an active agent in ovarian cancer [18]. As many as one third of treated patients with recurrent ovarian cancer may achieve an objective response [19, 20]. However, the standard 5-day treatment strategy is
often difficult for patients; the FDA-approved dose of 1.5 mg/m² per day for 5 days results in considerable bone marrow suppression, particularly in heavily pretreated patients.

Several noncomparative phase II trials and retrospective reviews of institutional experience in recurrent and resistant ovarian cancer have shown that it is possible to achieve reasonable objective response rates by employing a lower dose (1.0 or 1.25 mg/m²) during a 5-day treatment program [21–23], administering the drug on a 3-day regimen [24, 25] or delivering the agent on a weekly schedule [26–28]. In addition, these modified strategies result in a substantial reduction in the toxicities associated with use of topotecan in this palliative clinical setting.

**LIPOSOMAL DOXORUBICIN**

Similar to the experience with topotecan, the substantial toxicity (mucositis, stomatitis, and “hand-foot syndrome”) associated with the delivery of liposomal doxorubicin at the FDA-approved dose of 50 mg/m² on an every-4-weeks schedule [29, 30] has prompted investigators to examine alternative approaches for drug administration. Several reports have shown that at a liposomal doxorubicin dose of 40 mg/m² (delivered on an every-4-weeks schedule) [31–34], the objective response rate is similar to that achieved with the FDA-approved regimen (10%–15%), but with a substantially improved adverse-effect profile. These data provide strong support for the conclusion that, in the palliative setting, the lower-dose treatment program should be employed to optimize the chances for clinical benefit without excessive toxicity.

**BEVACIZUMAB**

Of considerable interest, several reports of single-agent bevacizumab employed as second-line therapy of ovarian cancer have revealed considerable activity for the agent (approximately a 15% objective response rate), including in individuals with well-characterized platinum-resistant disease [35–38]. Although a number of studies have also explored the use of bevacizumab in combination with chemotherapy in this clinical setting, there is currently no evidence that such regimens are superior to administration of the antiangiogenic agent alone [36].

In addition to the toxicities of bevacizumab noted in other clinical settings (e.g., severe hypertension), bowel perforation has been observed in 5%–10% of patients treated with this agent in ovarian cancer [38]. It has been suggested this serious adverse effect may be particularly relevant when bevacizumab is administered to patients with extensive intra-abdominal cancer present [38]. Further careful examination of this issue will be required to define the populations at risk and determine how this hazard may be minimized.

**OTHER FDA-APPROVED ANTI NEOPLASTIC AGENTS**

Several additional cytotoxic drugs approved for indications other than ovarian cancer may be reasonably employed by oncologists as a second-line strategy in this malignancy based on phase II clinical trial results where objective response rates of at least 10% have been reported in the peer-reviewed literature. These agents include irinotecan [39], vinorelbine [40–42], and oral etoposide [43, 44].

Three additional agents that have not as yet been approved by the FDA for administration outside the investigative setting are noteworthy for their possible future routine use in ovarian cancer. Trabectedin has shown particular promise in several trials in patients with sarcomas [45], and objective activity has also been documented in previously treated patients with ovarian cancer [46]. In clinical trials, TLK286, delivered as a single agent or as a component of a combination regimen, has demonstrated activity in platinum-resistant ovarian cancer [47]. The results of phase III trials exploring the utility of this drug in previously treated patients should be reported in the near future. Finally, the results of a randomized trial examining the effectiveness of a novel bispecific monoclonal anti-CD-3-anti-EpCAm antibody in the therapy of malignant ascites is anticipated with considerable interest. It is hoped that one or more of these agents will soon be available to oncologists to employ in the management of ovarian cancer.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

M.M. has acted as a consultant for Eli Lilly, Genentech, TBIT, GlaxoSmithKline, Cell Gene, TEB, Merck, and Wyeth.

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