Perspective

Recurrent Ovarian Cancer: How Important Is It to Treat to Disease Progression?

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ABSTRACT

Ovarian cancer is increasingly recognized as a chronic disease whose treatment is often characterized by administration of multiple, sequential active agents, each of which may or may not be accompanied by a tumor response. Despite the large proportion of patients who relapse and undergo longer-term treatment, the question of optimal treatment duration has not been fully addressed to date. For patients who progress on therapy, the answer is straightforward: they are switched to another active agent, presumably having a different mechanism of action from previous therapies with, ideally, limited overlapping toxicities. However, for patients who remain in partial response or who have stable disease, the answer is less apparent and less clear. The majority of oncologists believe that treatment beyond 6 cycles of a given therapy does not provide any additional benefit to patients. There are some data to support that treatment strategy. However, with the advent of new, less toxic agents, treatment to progression should be further explored. Agents that are potentially well suited for extended treatment intervals may include such properties as absence of cumulative toxicity, non–cross-resistance, positive benefit on quality of life, and convenient schedule. A number of active agents in ovarian cancer (platinum, paclitaxel, topotecan, liposomal doxorubicin, docetaxel, gemcitabine, and etoposide) will be reviewed in the context of what is known about cumulative toxicity, potential adverse effects on patients' quality of life, and evidence addressing the potential benefits of longer-term treatment.

INTRODUCTION

Ovarian cancer ranks fifth among the leading causes of cancer-related deaths in women and will account for an estimated 16,090 deaths in 2004 (1). Additionally, an estimated 25,580 new cases will be diagnosed, approximately 60% to 70% of which will be diagnosed at an advanced stage because of the lack of effective screening and early warning signs (1, 2). Treatment for advanced disease involves cytoreductive surgery followed by systemic treatment with paclitaxel and platinum or, alternatively, single-agent carboplatin. Overall tumor response rates associated with paclitaxel and platinum are relatively high and range from approximately 70% to 80% (3–6). However, 50% to 75% of responders will relapse within approximately 18 months after completing first-line therapy and require further systemic therapy (4).

Because only 10% to 15% of patients who present with advanced disease experience long-term remission, most patients are subject to repetitive treatment cycles, tumor responses and disease recurrences, or unchecked disease progression (7). Treatment of recurrent disease is palliative and is initiated with the goals of controlling disease-related symptoms, limiting treatment-related toxicity, maintaining or improving quality of life, delaying time to progression, and prolonging survival. Many active agents (platinum, paclitaxel, topotecan, liposomal doxorubicin, docetaxel, gemcitabine, and etoposide) are available that offer various clinical benefit-risk profiles.

Although many oncologists have embraced 6 cycles of chemotherapy as a typical or standard treatment duration, largely on the basis of clinical trials from front-line treatment (8), the limit of 6 cycles of a given regimen is not as rigorously supported in the recurrent disease setting. It is possible that patients with recurrent disease may benefit from extended treatment, provided their disease is stable or in partial response. This article will review the potential advantages and disadvantages of treating recurrent ovarian cancer patients until disease progression and will present a cataloging of the benefit-risk profiles of several active agents used in the treatment of this chronic disease. Opportunities and recommendations for further clinical investigations to prospectively address the issue of optimal treatment duration will be highlighted.

TREATMENT TO PROGRESSION: PROS AND CONS

Rationale Supporting Treatment to Progression

The rationale both for and against treating patients until disease progression is summarized in Table 1. There are several reasons for treating to progression, including the availability of a finite number of active agents, the importance of clinically significant symptom palliation and its associated effect on quality of life, and the importance of disease progression as a clinical end point (as it relates to triggering treatment decisions and effect on survival).

With the exception of paclitaxel and platinum chemotherapy (used in combination in the front-line treatment of patients

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Table 1 Treatment to progression rationale

Arguments for treatment to progression
Improves the management of a limited number of therapeutic options
Provides symptom palliation
Maintains stable disease
Newer agents have fewer cumulative toxicities
Arguments against treatment to progression
Lack of demonstrable benefits
Cumulative toxicity
Negative impact on quality of life and psychosocial issues
The use of more effective agents delayed

with ovarian cancer and in the retreatment of platinum-sensitive patients), only altretamine (hexamethylmelamine), liposomal doxorubicin, paclitaxel, and topotecan are approved by the United States Food and Drug Administration (FDA) for treatment of patients with ovarian cancer after initial or subsequent therapy fails. Furthermore, because ovarian cancer is increasingly approached as a chronic disease that frequently necessitates sequential treatment with several agents, a limited armamentarium plays an important role in long-term treatment planning. Limitations in the number of active agents in ovarian cancer management make it more important for oncologists to manage the available treatment options. New agents are needed that are active as monotherapy and in combination with existing treatments to increase the flexibility with which oncologists can implement a long-term strategic treatment plan. In the meantime, it may be argued that using existing agents as long as possible to control the disease may be prudent.

In the setting of what is essentially incurable disease (*i.e.*, patients with recurrent ovarian cancer with disseminated disease), effective palliative care is needed to enhance patients' quality of life. Although it is intuitive that recurrent ovarian cancer leads to a progressive decline in patients' quality of life, there is a virtual absence of reports on controlled, randomized studies in the medical literature addressing the quality of life effect of disease and the potential positive effects of active treatment. Nonetheless, anecdotal and case study evidence suggests that systemic treatment for advanced ovarian cancer provides benefits in symptom control. In other instances, investigators have inferred quality of life benefits from data from long-term treatment that demonstrate a lack of subjective toxic symptoms associated with extended treatment (9–11). For instance, two case reports of extended therapy with paclitaxel (11) and topotecan (10) suggested that patients achieved substantial quality of life benefits, at least in part attributed to the good tolerability of therapy. Furthermore, it is generally accepted that agents with fewer severe adverse effects (particularly cumulative adverse events) are associated with improved quality of life for patients. Unfortunately, no large, randomized, controlled trials have yet reported the effect of systemic chemotherapy on symptom palliation and quality of life in patients with relapsed ovarian cancer. Because quality of life is increasingly recognized as an important, underserved component of disease management in patients with gynecologic cancer, quality of life measures are increasingly included in clinical trial design, and many large, randomized trials are incorporating these measures as an important end point. Notably, quality of life assessment is planned in a phase III study of paclitaxel plus carboplatin for 6 cycles alone compared with paclitaxel plus carboplatin followed by 4 cycles of topotecan in previously untreated patients with advanced ovarian cancer (12). In an early report of that trial, there were no significant differences in nonhematologic toxicities in patients treated with paclitaxel plus carboplatin for 6 cycles alone compared with patients who received an additional 4 cycles of topotecan therapy (12). Although it was too early for quality of life assessment, the lack of additional or cumulative toxicity with >6 cycles suggested that newer agents with fewer cumulative toxicities may be appropriate for treatment to progression strategies.

Although it is more of a subjective rationale for treatment to progression, patients and their healthcare providers sometimes prefer a more active, if not aggressive, approach to controlling the disease as opposed to a "watchful waiting" approach. Active management of the disease may help to reduce the patient's anxiety that the disease is progressing unchecked. Another important issue associated with the "active approach" argument is the value of maintaining stable disease. The clinical value of stable disease has been demonstrated in a retrospective analysis of four multicenter topotecan trials (13). In that analysis, patients who achieved stable disease on therapy experienced a statistically significant survival benefit comparable with patients who achieved partial tumor response. In addition, a relatively high proportion of patients (17–63%) with recurrent ovarian cancer achieve stable disease as a best response (9, 14–20). However, the clinical benefits of stable disease may be underappreciated by both oncologists and patients (13). Although there is no direct evidence that treatment to progression may prolong the duration of stable disease, a prolonged duration of stable disease may assist in the palliation of symptoms and have a positive impact on quality of life.

It appears that a proportion of patients achieve a late (>6 courses of therapy) tumor response. The median time to best response has been reported to range from 6 to 7.5 weeks (approximately 2–3 cycles; ref. 17); however, some patients experience a late response. In a recent study of long-term therapy with topotecan, 3 of 12 patients (25%) who experienced a tumor response achieved remission after cycle 7 (9). In a phase II study, patients with platinum-resistant relapsed ovarian cancer received monthly liposomal doxorubicin (50 mg/m^2) for 6 cycles, with patients continuing on therapy if they were experiencing clinical benefit after 6 cycles (20). Twenty-eight patients (32%) received >6 cycles of therapy until disease progression, and the time to tumor response was up to 33 weeks. In a study of prolonged (12 cycles) platinum treatment compared with the standard 6-cycle treatment duration as first-line therapy, the progression-free survival was 30 months for patients treated with 12 cycles *versus* 15 months for patients receiving 6 cycles ($P = 0.0004$; ref. 21). Although the study was conducted in previously untreated ovarian cancer patients, and the proportion of patients who responded after 6 cycles of therapy was not specified, it can be inferred that a proportion of patients either responded late or had long-term stable disease. Unfortunately, the improved time to progression in longer-term treatment groups did not translate into a survival advantage in that study (21).

Rationale Against Treatment to Progression

In contrast to arguments for treating relapsed patients until disease progression, arguments against treating these patients to progression have revolved around poor tolerability and a lack of concrete evidence demonstrating the benefits of potentially longer-term treatment. Indeed, severe and/or cumulative toxicity may conspire to limit the dose and schedule of active agents or, alternatively, may lead to permanent discontinuation of therapy. The main toxicities, including potential cumulative toxicities for agents active in recurrent ovarian cancer, are summarized in Table 2 (19, 22–27). With few exceptions, agents used in advanced ovarian cancer are associated with cumulative toxicities that pose challenges to long-term treatment planning. Furthermore, with the introduction of each new agent, cumulative toxicities may result in a cycle of diminishing treatment options and render patients progressively less able to tolerate chemotherapy. For instance, retreatment with a platinum agent plus paclitaxel at first relapse may cause cumulative neurotoxicity and myelosuppression (23). Alternatively, treatment with liposomal doxorubicin may elicit cumulative palmar-plantar erythrodysesthesia (PPE) or cardiac/pulmonary adverse events (19, 26). Gemcitabine and topotecan, however, generally exhibit noncumulative myelotoxicity (17, 19, 24, 28). Treatment sequence should be carefully considered to allow the patient access to the most active agents while abrogating dose-limiting toxicity (29).

Perhaps the main objection to longer-term treatment is a notable lack of evidence supporting a clinical benefit. Although few studies have been performed to address the question of optimal treatment duration, the results of several reports have failed to establish a positive benefit of prolonged treatment on survival (8, 12, 21, 30). In an early, prospective, randomized trial comparing 10 cycles of cyclophosphamide, doxorubicin, and cisplatin (CAP) *versus* 5 cycles of CAP, patients treated with 10 cycles of CAP experienced greater myelosuppression, nephrotoxicity, and neurotoxicity than those receiving 5 cycles of CAP. Additionally, there was no difference in survival between the two groups ($P = 0.41$; ref. 8). In a similar trial conducted by Gershenson *et al.* (21), the overall survival of patients treated with 12 cycles of cisplatin/cyclophosphamide (29 months) was not statistically different from that of patients who received 6 cycles of cisplatin/cyclophosphamide (35

Table 2 Summary of grade 3 or 4 toxic events and cumulative toxicities of chemotherapeutic agents for advanced ovarian cancer*

	Toxicities		
Agent (ref. no.)	Hematologic (%)	Nonhematologic (%)	Cumulative
Carboplatin (22)	Thrombocytopenia (16) Leukopenia (10) Anemia (1)	Nausea/vomiting (9) Alopecia (4) Renal (1) Neurologic (1) Hepatic (<1) Cardiovascular (<1)	Thrombocytopenia
Cisplatin (23)	Granulocytopenia (48) Anemia (11) Thrombocytopenia (4)	Nausea/vomiting (33) Neurologic (11) Renal (4) Cardiovascular (2)	Renal toxicity Neurotoxicity High-tone hearing loss
Paclitaxel (23)	Granulocytopenia (96) Anemia (6) Thrombocytopenia (3)	Nausea/vomiting (10) Fever (3) Cardiovascular (2) Neurologic (1)	Peripheral neurotoxicity
Weekly paclitaxel (25)	Neutropenia (18) Anemia (4) Thrombocytopenia (0)	Nausea/vomiting (4) Arthralgia/myalgia (5) Neuropathy (11)	Peripheral neurotoxicity (lower incidence than every 3-weeks regimen)
Topotecan (19)	Neutropenia (77) Leukopenia (50) Thrombocytopenia (34) Anemia (28)	Alopecia (6) Stomatitis (<1)	Possible fatigue
Liposomal doxorubicin (19)	Neutropenia (12) Leukopenia (10) Anemia (5) Thrombocytopenia (1)	PPE (23) Stomatitis (8) Alopecia (1)	PPE Mucositis Cardiotoxicity
Gemcitabine (24)	Leukopenia (22) Thrombocytopenia (12)	Nausea/vomiting (12) Flu-like symptoms (4) Peripheral edema (2) Lethargy (2) NCPE (rare)	None
Etoposide (27)	Neutropenia (45) Leukopenia (41) Anemia (13) Thrombocytopenia (9)	Nausea/vomiting (15) Neurologic (2)	Secondary leukemia

Abbreviations: PPE, palmar-plantar erythrodysesthesia; NCPE, noncardiogenic pulmonary edema.
* Adapted with permission from Dunton (26).

months). Overall survival in that trial was comparable between the two groups, despite a significant ($P = 0.0004$) improvement in time to disease progression in patients treated with 12 cycles (30 *versus* 15 months). In addition, there was no difference in response, progression-free survival, or survival between previously untreated patients who received 6 cycles of carboplatin/paclitaxel and patients who received 6 cycles of carboplatin/paclitaxel followed by 4 cycles of topotecan (12). Likewise, in a review of three randomized trials conducted in previously untreated patients, Bertelsen *et al.* (31) found no relationship between the number of courses or cumulative dose and tumor response. Taken together, the results of these studies fail to provide convincing evidence that extended treatment durations improve survival outcomes.

Further clarification is needed about the selection of patients and therapies for treatment to progression before the relative benefits can be thoroughly assessed. For example, 12-month consolidation therapy with paclitaxel significantly prolonged survival for patients whose disease completely responded to platinum and paclitaxel-based therapy (32), but 4-month consolidation therapy with topotecan did not improve progression-free survival in patients who had partial or complete responses to platinum and paclitaxel-based therapy (33). Whether this agent is ineffective as a maintenance therapy or whether only 4 additional cycles are too few to demonstrate the very large survival advantage that would be necessary to produce a detectable effect in this study is unknown. However, the benefits of long-term therapy in patients with multiple relapse and bulky disease may differ from those in the consolidation therapy setting. Another area that requires further study is whether rising CA 125 levels alone are indicative of cancer progression or whether treatment should be discontinued only when disease progression is visible through imaging. Clearly, additional trials are needed to fully assess the clinical value of extended systemic treatment, especially in patients with recurrent disease.

Finally, the temptation to continue patients on a therapy that has yielded a tumor response or stable disease as a best response may delay the switch to another, more efficacious agent. In this scenario, agents with novel mechanisms of action and nonoverlapping toxicity, with potentially different resistance patterns, may be used suboptimally or at subtherapeutic dose levels. The optimal sequence of agents in advanced ovarian cancer therapy has not been determined, although the subject has been reviewed recently by Armstrong (29). Nevertheless, several agents have been characterized in recurrent ovarian cancer, and each of these agents will be discussed in the following section.

BENEFIT-RISK RATIO OF CHEMOTHERAPY IN RECURRENT OVARIAN CANCER

Patients who experience disease relapse or who are refractory to first-line treatment are candidates for second-line chemotherapy. Important considerations for an agent used in this setting (and potentially over the longer term) are summarized in Table 3. An ideal agent will provide broad antitumor activity, demonstrate a favorable toxicity profile, and have generally convenient administration, among other factors. Additionally, many of the more active agents used in second-line treatment (*e.g.,* gemcitabine, liposomal doxorubicin, and topotecan) are non–cross-resistant to first-line therapies. They exhibit novel mechanisms of action relative to cisplatin/carboplatin and paclitaxel, thereby targeting a different aspect of cell division. Although no agent fits the model of an ideal agent in all characteristics, several have favorable profiles (Table 4; refs. 14–20, 34–57). These agents include members of the platinum and taxane families, such as carboplatin and paclitaxel (every 3 weeks and weekly schedules), respectively; the topoisomerase I inhibitor topotecan; the liposome-encapsulated anthracycline doxorubicin (liposomal doxorubicin); and the novel antimetabolite gemcitabine. The clinical utility (benefit-risk ratio) of these agents in the recurrent ovarian cancer setting will be reviewed briefly below.

Table 3 Characteristics of an ideal chemotherapeutic agent for long-term treatment of recurrent ovarian cancer

Activity in platinum- and paclitaxel-sensitive and -resistant tumors
Absence of cumulative toxicities
Non—cross-resistant to other agents
Provides symptom palliation
Offers quality-of-life benefits
Convenient administration schedule

Hexamethylmelamine

Hexamethylmelamine (altretamine; Hexalen; MGI Pharma, Bloomington, MN) is an approved single-agent therapy for ovarian cancer. It has the advantage of oral administration, which may be preferable for some patients. However, it has demonstrated only limited activity in patients with relapsed platinum-refractory ovarian cancer (58).

Platinum

Patients who were found to be platinum sensitive in first-line therapy are likely to benefit from reintroduction of platinum on disease recurrence. Both cisplatin (Platinol; Bristol-Myers Squibb, Princeton, NJ) and carboplatin (Paraplatin; Bristol-Myers Squibb) are FDA-approved for the treatment of recurrent ovarian cancer and are often used as monotherapy or in combination with paclitaxel. Carboplatin is considerably less nephrotoxic than cisplatin; however, because the primary route of clearance is renal, the potential for acute renal toxicity should be monitored when establishing the dosage. In clinical trials of single-agent carboplatin, overall tumor response rates ranged from 21% to 30% in platinum-resistant or platinum-refractory patients and from 27% to 53% in platinum-sensitive patients (34–37). Furthermore, the proportion of patients with stable disease was approximately 18% to 33%.

Myelosuppression characterized by thrombocytopenia and granulocytopenia is dose-limiting, and platelet toxicity in particular can occur frequently and may be severe and cumulative (59–61). Additionally, there is significant risk for neurotoxicity and hypersensitivity reactions, with 12% of patients experiencing allergic hypersensitivity in one trial (62). Cumulative toxicities associated with cisplatin include dose-dependent renal tubule toxicity and neurotoxicity (63).

Table 4 Characteristics of active agents in recurrent ovarian cancer

Agent (ref. no.)	Mechanism of action	Efficacy outcomes	Main toxicity
Carboplatin (34–37)	DNA cross-linking	ORR, 21–53% (sensitive, 27–53%; refractory, 21–30%) Median TTP, >7–22.5 mo Median survival, 7.9–12 mo	Myelosuppression (thrombocytopenia)
Paclitaxel, every 3-weeks regimen (17, 46–51)	Microtubule stabilizer	ORR, 13–45% (sensitive, 45%; refractory, 19–22%) Median TTP, 3–9 mo Median survival, 6–26 mo	Myelosuppression, neurotoxicity
Paclitaxel, weekly regimen (52–54)	Microtubule stabilizer	ORR, 27–56% (refractory, 27–56%) Median TTP, 4 mo Median survival, 10–13.7 mo	Myelosuppression, neurotoxicity
Paclitaxel/carboplatin (14, 55)		ORR, 70–84% (sensitive) Median TTP, 9.7–13 mo Median survival, 13.1–27+ mo	
Topotecan (15, 16, 18, 56, 57)	Topoisomerase I inhibition	ORR, 14–33% (sensitive, 33%; resistant, 14–18%) Median TTP, 2.7–10.8 mo Median survival, 10–20.2 mo	Myelosuppression
Liposomal doxorubicin (19, 20, 44, 45)	Nucleic acid synthesis inhibition	ORR, 16–26% (refractory, 16–26%) Median TTP, 3.7–5.7 mo Median survival, 11–14 mo	PPE stomatitis
Gemcitabine (39–43)	Nucleoside analogue	ORR, 13–22% (refractory, ~19–22%) Median TTP, 2.8–6.6 mo Median survival, 6.2–9 mo	Myelosuppression, hepatic
Docetaxel (38)	Microtubule stabilizer	ORR (resistant), 22.4%	Myelosuppression (neutropenia)
Etoposide (27)	Topoisomerase II inhibitor	Sensitive: ORR, 34%; median survival, 16.5 mo Refractory: ORR, 27%; median survival, 10.8 mo	Myelosuppression

Abbreviations: ORR, overall response rate; TTP, time to progression; PPE, palmar-plantar erythrodysesthesia.

Although cisplatin and carboplatin are associated with risks for cumulative toxicity, long-term treatment with cisplatin has been pursued in a previously untreated ovarian cancer population. In a study by Gershenson *et al.* (21), progression-free survival was 30 months for patients treated with 12 cycles of cisplatin *versus* 15 months for patients treated with 6 cycles of cisplatin ($P = 0.0004$). Unfortunately, the advantage of longer-term treatment on time to progression failed to translate into a survival benefit in that study (21). Although the toxicity profile in the cisplatin treatment groups was not reported in that study, the investigators suggested that carboplatin may be more feasible for long-term use because of its convenient outpatient administration and generally favorable tolerability profile. However, the feasibility of prolonged use of carboplatin in patients with recurrent disease remains to be determined. Long-term use of either of these platinums is associated with an increased risk of hypersensitivity reactions (64).

Gemcitabine Plus Platinum

Gemcitabine (Gemzar; Eli Lilly and Co., Indianapolis, IN) has received approval in other indications but is still investigational in the treatment of ovarian cancer. Gemcitabine can be safely combined with carboplatin for the treatment of patients with relapsed ovarian cancer (65). The gemcitabine plus carboplatin regimen recently compared favorably with carboplatin alone in a randomized trial in patients with relapsed platinum-sensitive ovarian cancer, producing significant improvements in quality of life, significantly faster palliation of abdominal symptoms, significant improvements in response rate, and a significant increase in progression-free survival (66). These data, along with the results from the International Collaborative Ovarian Neoplasm (ICON4) clinical trial, (67, 68) are the first demonstrations of survival superiority using a combination regimen *versus* single-agent therapy in the relapsed platinum-sensitive ovarian cancer setting. However, a greater proportion of patients who received the combination therapy required hematologic growth factor support and red blood cell transfusions compared with patients who received carboplatin alone (66). A preliminary report of a phase II trial of gemcitabine plus oxaliplatin suggests that this combination has promising activity and is associated with only mild to moderate toxicity in heavily pretreated patients with relapsed ovarian cancer (69). Further investigations are needed to determine the efficacy of gemcitabine plus platinum combination therapies in patients with refractory disease and whether these combinations are appropriate for long-term treatment.

Paclitaxel

Every 3 Weeks. Paclitaxel (Taxol; Bristol-Myers Squibb) is indicated as first-line (with cisplatin or carboplatin) and

subsequent therapy for the treatment of ovarian cancer. The taxane is administered in two different schedules; however, the FDA-approved dosing is intravenous administration over 3 or 24 hours once every 3 weeks. In studies of paclitaxel administered on this schedule, overall tumor response rates were approximately 22% in platinum-resistant or platinum-refractory patients and 45% in platinum-sensitive patients (46, 50, 51). Median survival in platinum-resistant or -refractory patients ranged from 6 to 9 months and was 26 months in 47 evaluable platinum-sensitive patients. In studies of mixed platinum sensitivity, the overall response rates ranged from 13% to 20% (17, 47–49). Approximately 19% to 54% of patients receiving paclitaxel experience stable disease as a best response, whereas 24% to 59% of patients receiving paclitaxel progress on therapy (17, 46–51).

The main toxicities associated with paclitaxel include myelosuppression and peripheral neuropathy. The dose-limiting toxicity is myelosuppression, especially in heavily pretreated patients; however, other common adverse events include allergic hypersensitivity reactions, alopecia, nausea and vomiting, diarrhea, and mucositis (23). Prophylactic pretreatment to decrease the risk of hypersensitivity is routine for patients receiving paclitaxel. This regimen involves dexamethasone (20 mg orally 12 hours before and 6 hours before paclitaxel or a single 20-mg dose intravenously 30 minutes before paclitaxel) in conjunction with both H(1) and H(2) receptor antagonists (*e.g.,* ranitidine and diphenhydramine) and antiemetic therapy. Recent evidence suggests that the conventional oral dosing regimen of dexamethasone may be more effective than the single-dose intravenous treatment (70). Dexamethasone can have short-term adverse effects on salt and water retention, glucose tolerance, and susceptibility to some infections and can lead to cumulative effects such as myopathy (71). Peripheral neuropathy associated with paclitaxel therapy may be cumulative and may have a profound adverse effect on patient quality of life (72).

The toxicity profile of paclitaxel administered every 3 weeks is generally less favorable than it is when the agent is administered weekly; therefore, partly because of the sometimes debilitating toxicity associated with the approved schedule, investigators have developed interest in evaluating the antitumor activity and tolerability of weekly schedules.

Weekly. Although weekly paclitaxel is not an approved regimen in ovarian cancer therapy, overall tumor responses were at least comparable and potentially higher than those achieved with the every-3-weeks schedule in preliminary studies in patients with recurrent disease (25). In a randomized, comparative study of paclitaxel weekly (paclitaxel, 67 mg/m^2/week) *versus* every 3 weeks, the overall response rates were the same for both treatment groups (41%; ref. 25). In other studies of weekly paclitaxel (80 mg/m^2), overall tumor response rates ranged from 25% to 62% in platinum-resistant or -refractory patients (52–54, 73) and 59% in one small study ($n = 17$ evaluable patients) in a predominantly platinum-sensitive patient group (74). Median survival was approximately 10 to 12 months.

The main toxicities of weekly paclitaxel were similar to those of paclitaxel administered every 3 weeks, although at a slightly lower frequency and severity, and dexamethasone-based premedication was also required. In a randomized trial directly comparing weekly *versus* every-3-weeks administration schedules, there was a significantly ($P < 0.001$) lower incidence of grade 3/4 neutropenia in the weekly treatment group (18% *versus* 45%, respectively; ref. 25). Moreover, weekly paclitaxel was associated with a significantly ($P < 0.001$) lower incidence of grade 3 neuropathy (11% *versus* 29%). Additionally, in noncomparative trials, weekly administration appears to cause less neutropenia and peripheral neuropathy than historically reported frequencies with the standard schedule (47–49). Thus, weekly paclitaxel may increase the probability of a patient achieving a beneficial tumor response with fewer adverse events and cumulative neurotoxicity.

Platinum Plus Paclitaxel

Patients who responded to combination first-line therapy may benefit from reintroduction of platinum and paclitaxel on disease recurrence. In the largest study to date conducted in collaboration with the International Collaborative Ovarian Neoplasm (ICON4) and three cooperative groups, 802 relapsed patients with ovarian cancer were randomized to treatment with platinum plus a taxane or single-agent platinum (67). Overall tumor response rate in the combination group was 66% compared with 54% in the platinum treatment group ($P = 0.06$). Notably, the hazard ratios for progression-free survival and overall survival were 0.76 and 0.82, respectively, favoring platinum plus paclitaxel over single-agent platinum in both cases. Thus, there was a statistically significant difference in survival favoring the platinum plus paclitaxel combination compared with single-agent platinum ($P = 0.023$; ref. 67).

In other clinical trials of combination platinum plus paclitaxel, overall tumor response rates in platinum-sensitive patients ranged from 70% to 84%, although these were biochemical responses (14, 55). An additional 8% to 17% of patients had stable disease. Median survival of platinum-sensitive patients retreated with paclitaxel plus carboplatin was 13 months in one retrospective study ($n = 84$ evaluable patients) and >27 months in a second retrospective case review ($n = 43$ evaluable patients; refs. 14 and 55). In one small subset of patients who were refractory to platinum, the response rate was 38%, and the median time to progression was 3.2 months (75).

Although reintroduction of carboplatin plus paclitaxel is highly effective in patients sensitive to platinum administered as first-line therapy, treatment with these agents can result in cumulative neurotoxicity and myelosuppression, which may limit treatment options on subsequent recurrences. Carboplatin is associated with progressive myelosuppression (particularly thrombocytopenia) and allergic reaction, and paclitaxel is associated with cumulative neurotoxicity. Furthermore, the combination regimens (carboplatin with paclitaxel or gemcitabine) fail to exclude the possibility that sequencing these agents may be equally as effective, with perhaps less toxicity. Additional trials are planned through the Gynecologic Oncology Group to examine this issue. For example, a proposed trial will compare the efficacy and safety of six different platinum-based combination therapy regimens, one of which will contain sequential therapy with a platinum agent followed by a taxane, in patients with ovarian cancer who will have been randomized to receive secondary cytoreduction surgery initially or no surgery before chemotherapy.

Topotecan

Topotecan (Hycamtin; GlaxoSmithKline, Philadelphia, PA) is an active and well-established agent currently indicated [topotecan (1.5 mg/m^2) on days 1 through 5 of a 21-day cycle] for the treatment of relapsed metastatic ovarian cancer after failure of initial or subsequent chemotherapy. In several large phase II trials of patients with advanced ovarian cancer, tumor response rates ranged from 14% to 33% (15, 16, 18, 56, 57). In platinum-sensitive patients, defined as those patients relapsing ≥6 months after completing platinum therapy, overall tumor response rates ranged from 19% to 33% (16, 18, 57). Additionally, topotecan is active in platinum-refractory patients, yielding tumor response rates of 14% to 18% (15, 16, 56, 57). Stable disease was achieved in an additional 18% to 48% of patients receiving topotecan in these trials. In a trial conducted in platinum-sensitive patients, median survival had not been reached at a follow-up of 21.5 months (18). The main severe toxicity associated with topotecan is reversible, noncumulative neutropenia. Although the main toxicity is myelosuppression, the need for growth factor support, platelets, and red blood cell transfusions did not increase with the duration of topotecan treatment (9). The nonhematologic toxicity profile of topotecan is generally favorable, with the topotecan dose level rarely limited because of nonhematologic toxicity. A recent analysis of clinical trial data for topotecan in the small-cell lung cancer setting found that elderly patients may be at higher risk for developing diarrhea during treatment.[1] Fatigue, a common side effect of chemotherapy in patients with advanced cancer, may become severe during extended therapy. Alternative dosing and scheduling of topotecan are currently investigational and may provide additional treatment options in heavily pretreated patients (76).

Because the neutropenia observed with topotecan is noncumulative and the nonhematologic toxicity is rarely dose-limiting, there has been interest in evaluating the potential of longer-term therapy (9). McGuire *et al.* (18) first demonstrated the utility of prolonged topotecan in platinum-sensitive patients at relapse. In that study, a median of 6 cycles of topotecan was administered; consequently, a large proportion of patients continued on therapy beyond 6 cycles, with some receiving as many as 18 cycles. This finding, in part, is attributed to the high percentage of patients who achieved objective tumor response (33%) or stable disease (48%) as their best response. However, 9 of 15 patients who responded to topotecan elected to discontinue therapy before progression because of fatigue. In a second study of prolonged topotecan therapy, 33 patients with recurrent disease received a mean of >10 courses of therapy (9). Of 32 patients evaluable for response, 12 patients (1 patient with complete response and 11 patients with partial responses) achieved an objective tumor response (38%), and 20 patients (63%) had stable disease as a best response.

Liposomal Doxorubicin

Liposomal doxorubicin (Doxil; Ortho Biotech, Bridgewater, NJ) is an active agent indicated for the treatment of patients with disease that is refractory to both paclitaxel- and platinum-based regimens. The largest trial experience with liposomal doxorubicin in recurrent ovarian cancer was reported by Gordon *et al.* (19). Patients were randomized to receive liposomal doxorubicin (50 mg/m^2) once every 4 weeks or topotecan (1.5 mg/m^2/day) for 5 consecutive days every 3 weeks. The overall tumor response rate was similar in the two treatment groups [19.7% (liposomal doxorubicin) *versus* 17.0% (topotecan); $P = 0.390$]. In the intent to treat population, median overall survival was 60 weeks in liposomal doxorubicin-treated patients and 56.7 weeks in topotecan-treated patients ($P = 0.341$). Differences were seen in survival among the subgroups. In platinum-sensitive patients, survival times were statistically significantly longer in liposomal doxorubicin-treated patients compared with topotecan-treated patients (108 *versus* 71.1 weeks; $P = 0.008$). In contrast, survival tended to favor topotecan treatment in platinum-resistant patients (41.3 *versus* 35.6 weeks), although the difference was not statistically significant ($P = 0.455$). Survival data should be interpreted with caution because survival was not a primary end point in the study and the investigators did not account for treatment crossover.

In an earlier trial conducted by Gordon *et al.* (20) in primarily platinum-resistant or platinum-refractory patients, the overall tumor response rate was 17%, with an additional 40% of patients experiencing stable disease as a best response. Notably, in other phase II trials conducted in platinum-refractory patients, liposomal doxorubicin (50 mg/m^2) administered once every 3 or 4 weeks led to overall tumor response rates ranging from 16% to 26% (44, 45). Although hematologic toxicity is common and may on occasion be dose-limiting, the myelosuppression is usually transient and noncumulative. Liposomal doxorubicin is rarely associated with cardiovascular toxicity, unless patients have cardiovascular comorbidities. The main severe (grade 3/4) toxicity associated with liposomal doxorubicin is PPE, which occurs in approximately 20% to 30% of patients (19, 20, 45). Because PPE tends to progressively worsen with the number of cycles administered and there is no established pharmacological intervention for this condition, longer-term therapy with the agent has not been commonly practiced. However, liposomal doxorubicin at 40 mg/m^2 appears to have similar activity and decreased toxicity compared with the 50 mg/m^2 dose (77), and PPE and stomatitis are generally mild to moderate in severity at this reduced dose level (78). Although it remains to be seen, perhaps this lower dose of liposomal doxorubicin has a role in longer-term therapy.

Similar to clinical initiatives with other novel agents, many trials are ongoing or planned to evaluate liposomal doxorubicin in various combination regimens, including regimens containing platinum, gemcitabine, and topotecan. Preliminary evidence suggests that tumor response rates may be improved further when liposomal doxorubicin is combined with other active agents (43, 79).

Docetaxel

Although docetaxel (Taxotere; Aventis Pharmaceuticals Inc., Bridgewater, NJ) is more commonly used in the treatment of non–small-cell lung cancer and breast cancer, recent studies have been conducted in patients with relapsed ovarian cancer (38, 80). In the largest study, with 60 paclitaxel-resistant ovarian cancer patients receiving docetaxel (100 mg/m^2) every 21 days,

[1] J. Garst, personal communication.

Rose *et al.* (38) reported a response rate of 22%, including 5% and 17% complete and partial response rates, respectively. In a preliminary study of docetaxel administered in a biweekly schedule, two of nine enrolled patients achieved a tumor response (one complete response and one partial response; ref. 80). Myelosuppression is the main toxicity associated with docetaxel, with up to 75% of patients experiencing grade 4 neutropenia (38). Additionally, 36% of patients required dose reductions attributed to toxicity. Fluid retention, particularly peripheral edema, occurs in many patients and may be severe, especially in patients who receive high cumulative doses of docetaxel (81). Because of the cumulative nature of its toxicity, the 100 mg/m^2 docetaxel dose level may not be optimal for heavily pretreated patients, and investigations of lower dosing levels in this setting are needed. However, in contrast to paclitaxel, docetaxel is associated with a lower incidence of neuropathy and hypersensitivity, which may make this agent more appealing for use in combination with platinum agents.

The potential role of docetaxel-based combination regimens has not been rigorously evaluated. However, tumor response rates of 75% were reported in 30 previously treated patients with ovarian cancer receiving docetaxel + carboplatin (82). Median time to progression was 9.4 months in that study. Of importance, the addition of docetaxel to platinum therapy did not increase the incidence or severity of neurotoxicity.

Gemcitabine

Although not currently FDA-approved for the treatment of ovarian cancer, gemcitabine (Gemzar; Eli Lilly and Co.) has typically been administered as monotherapy in heavily pretreated patients with ovarian cancer. In several phase II trials of largely platinum-resistant or -refractory patients, gemcitabine administered weekly at doses ranging from 800 to 1,250 mg/m^2 yielded overall tumor response rates of 13% to 22% (39–43). Studies of single-agent gemcitabine are rare in platinum-sensitive patients because, heretofore, the agent has typically been reserved until patients are refractory to platinum and other agents used in the treatment of relapsed disease. Gemcitabine is very well tolerated, and there are no cumulative myeloid toxicities. The majority of hematologic and nonhematologic adverse events are mild to moderate in severity. Additionally, once-weekly dosing is generally a convenient schedule for patients.

Because of the ability of gemcitabine to be synergistic, especially with platinum compounds, there has been a significant level of active research with gemcitabine-based combination regimens (83). Recent data have suggested that gemcitabine may have a possible role in overcoming platinum resistance by its inhibition of excision repair enzymes (84). The results of smaller phase II trials also suggest that either liposomal doxorubicin or topotecan administered in conjunction with gemcitabine improves tumor response rates compared with historical results observed with single agents (85, 86). Gemcitabine is non–cross-resistant to other agents, is generally well tolerated, has an absence of cumulative toxicity, and is convenient. Additional studies are needed to determine whether gemcitabine is suitable for longer-term treatment of advanced, recurrent ovarian cancer.

Etoposide

Etoposide (VePesid; Bristol-Myers Squibb) inhibits topoisomerase II and thus inhibits DNA synthesis. In a phase II study in patients with recurrent ovarian cancer, Eckhardt *et al.* (87) investigated etoposide (150 mg/m^2) on days 1 through 3 of a 28-day cycle. Of the 71 patients evaluable for response, 1 achieved a complete response, and 5 achieved a partial response. An additional 48 patients had stable disease. Myelosuppression was the main toxicity, with 26 patients experiencing grade 2 or 3 anemia. Patients also experienced grade 2 and 3 nausea and vomiting. In another phase II study, prolonged oral etoposide was studied in ovarian cancer patients with refractory or resistant disease (88). In that study, patients received etoposide (50 mg/m^2) daily for 21 days, followed by 7 days of rest. Of the 25 evaluable patients, 4 had a partial response. Myelosuppression was the major toxicity, resulting in a median dose intensity of 83% overall cycles. Similarly, Rose *et al.* (27) more recently investigated prolonged oral etoposide in both platinum-sensitive and platinum-resistant patients. Etoposide (50 mg/m^2) for 21 days every 28 days was active in both platinum-sensitive and platinum-resistant patients with an overall response rate of 34% and 27%, respectively. Grade 3 or 4 hematologic toxicity was common. In addition, one patient developed leukemia. Unfortunately, higher cumulative doses and longer therapy with etoposide are associated with the development of secondary myelodysplasia and acute leukemias (89). Therefore, given the existence of other agents without cumulative toxicity, it appears that etoposide may not be an appropriate agent for treatment to progression.

Other Novel Agents

A number of new compounds such as biologics [*e.g.,* bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA)], novel platinum analogs [*e.g.,* oxaliplatin (Eloxatin; Sanofi-Synthelabo, New York City, NY)], and novel taxane-based agents [*e.g.,* CTI-2103 (Xyotax; Cell Therapeutics, Inc., Seattle, WA) and ABI-007 (Abraxane; American Pharmaceutical Partners, Inc., Schaumburg, IL)] are under development and either are or will be included shortly in ovarian cancer clinical trials.

FUTURE DIRECTIONS AND CONCLUSIONS

Randomized, controlled trials have failed to demonstrate an improvement in survival for patients with recurrent ovarian cancer who received extended therapy. However, some studies have suggested that continuous treatment in patients who achieve a response to therapy may delay time to disease progression, which may be associated with a clinical benefit. Clearly, additional work is needed to address the treatment to progression question.

There are several important avenues for further investigation. Limited data are available in the medical literature that address the palliative efficacy of systemic chemotherapy in advanced, recurrent ovarian cancer. Data from large, randomized, controlled trials detailing the effect of systemic chemotherapy on symptom palliation and quality of life are limited. The quality of life data from the large phase III Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Group

d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) trial investigating paclitaxel + carboplatin followed by topotecan in previously untreated patients are eagerly awaited (12). Additional refinement in the care of patients with symptomatic metastatic foci should be possible with the use of quality of life instruments in future clinical trials. In addition, because of the aggressive nature of ovarian cancer, cumulative toxicities and disease progression may conspire to limit the choice and duration of treatment. Treatments with improved tolerability profiles will help facilitate longer-term treatment. Although agents with no known cumulative toxicities are available, additional active agents with novel mechanisms of action and favorable safety profiles are clearly needed. Studies are needed that would evaluate potential strategies for providing long-term stable disease or durable tumor response. The introduction of new agents or the redesign of doses and schedules of existing agents is a means to increase the efficacy of therapy and delay disease progression. Importantly, the recent emergence of combination therapy data in the platinum-sensitive recurrent disease setting raises the issue of whether the optimal approach to treating these patients may involve concomitant combination therapy or regimens that combine established and novel chemotherapeutic agents sequentially.

In conclusion, the questions of optimal treatment duration and whether patients should receive treatment to disease progression remain unanswered. However, in the absence of definitive evidence addressing optimal treatment duration in patients with relapsed disease, it should be recognized and appreciated that a number of agents are available that offer a level of flexibility and treatment customization heretofore unseen in the management of recurrent ovarian cancer in this generally poor-prognosis patient population. These agents should be wielded with the critical goal of balancing the efficacy and toxicity of particular agents and schedules with their effect on symptoms and quality of life.

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