Ovarian Cancer: Medical Management Approaches Today and Tomorrow

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Introduction

Each year, ovarian cancer affects more than 23,000 women and accounts for approximately 14,000 deaths in the United States.[1] In Western and Northern Europe, as well as in the United States, it is the fifth leading cause of cancer death among women and is the most deadly of the gynecologic malignancies.[2] Although the annual incidence of ovarian cancer is only 17 cases per 100,000 women overall, the incidence is much higher in older women, with a peak age-adjusted rate of 54 per 100,000 in women 75 to 79 years old.[3] The median age at diagnosis is 61 years.[1] Patients with familial ovarian cancer -- which represents about 5% to 10% of cases -- tend to be diagnosed almost a decade earlier.

The most important risk factor for the development of ovarian cancer is having a known genetic predisposition or a family history of a first-degree relative. Women who are carriers of germ-line mutations of the BRCA1 and BRCA2 genes have a range of 16% to 40% estimated risk of developing ovarian cancer by the age of 70 years, compared with a lifetime risk of 1.73% in the general population.[1,4,5]

Approximately 70% of women present with advanced disease. Most will respond to initial therapy; however, the relapse rate is high, and the 5-year survival of patients with advanced disease is 25% to 35%.[6,7] Favorable prognostic factors include young age, cell type other than clear cell or mucinous, lower stage, good performance status, small residual tumor volume, and absence of ascites.[8,9] Of note, patients with BRCA1 mutations may have a more favorable prognosis than those without this mutation.[10]

First-line Therapy

Establishing the Standard of Care

The combination of cisplatin and paclitaxel was established as first-line therapy for advanced ovarian cancer in the mid-1990s after a large, phase 3 Gynecologic Oncology Group (GOG) trial demonstrated superior results with this combination vs the then-standard regimen of cyclophosphamide and cisplatin.[11]

In this trial, 410 women with stage III epithelial ovarian cancer who had a large residual tumor (defined as > 1 cm) after surgery and those with stage IV disease were randomized to receive 1 of 2 regimens: cisplatin 75 mg/m^2 intravenously plus cyclophosphamide 750 mg/m^2 intravenously, or cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 intravenously as a 24-hour continuous infusion. The overall response rates were 60% in the cyclophosphamide/cisplatin arm and 73% in the paclitaxel/cisplatin arm, with a significantly higher complete response rate in the paclitaxel/cisplatin arm than in the cyclophosphamide/cisplatin arm (51% vs 31%). Furthermore, the progression-free survival was significantly longer in the paclitaxel/cisplatin arm (18 months) compared with the cyclophosphamide/cisplatin arm (13 months), as was the overall survival (38 months vs 24 months, respectively).

A European-Canadian Intergroup trial in which paclitaxel was given at a dose of 175 mg/m^2 over a 3-hour period to 688 women sought to confirm these results.[12] As with the GOG trial, the overall and complete response rates and the progression-free and overall survival rates were significantly higher in the paclitaxel/cisplatin arm vs the cyclophosphamide/cisplatin arm. However, the incidence of grade 3 neurotoxicity was significantly higher in the

paclitaxel/cisplatin group (19%) vs the cyclophosphamide/cisplatin group (4%). Moreover, this incidence appeared to be much higher than the 4% incidence observed in the paclitaxel/cisplatin arm of the GOG study.[11] This was thought to be due to the 3-hour infusion of paclitaxel since investigators at the Cleveland Clinic observed a similar rate of neurotoxicity (18% grade 3 and 3% grade 4) with a 3-hour infusion of paclitaxel (135 mg/m^2 or 175 mg/m^2) when combined with cisplatin.[13] Currently, the 24-hour infusion of paclitaxel is recommended if the combination of paclitaxel and cisplatin is to be used.[14]

A number of studies have evaluated the combination of paclitaxel and carboplatin as an alternative to the paclitaxel and cisplatin regimen. This combination is attractive because it is associated with a lower incidence of nonhematologic toxicities (particularly neurotoxicity), and it allows for outpatient administration.[15,16]

A large study conducted by the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) study group randomized 798 women with stage IIB through stage IV ovarian cancer to paclitaxel 185 mg/m^2 intravenously over 3 hours plus either cisplatin 75 mg/m^2 or carboplatin dosed to achieve an area under the curve (AUC) of 6.[17] After a median follow-up time of 100 weeks, there were no differences observed between the 2 groups in terms of progression-free survival or overall survival. Similarly, response data in a subset of 158 patients with measurable disease showed no differences in the overall or complete response rates.

Hematologic toxicities were more frequent in the paclitaxel/carboplatin arm, with grade 3 or 4 neutropenia occurring in 14% of patients vs 8% of patients in the paclitaxel/cisplatin arm. By contrast, nonhematologic toxicities were significantly more common in the paclitaxel/cisplatin arm, with 19% of patients in this arm showing grade 3 or 4 peripheral neuropathy vs 8% in the paclitaxel/carboplatin arm. In addition, patients treated in the paclitaxel/carboplatin arm had a significantly better quality of life.[17]

In a second study examining this regimen, 840 patients with stage III disease were enrolled, 798 of whom were evaluable.[18] Patients were randomized to receive paclitaxel 135 mg/m^2 as a 24-hour infusion plus cisplatin 75 mg/m^2 or paclitaxel 175 mg/m^2 over 3 hours plus carboplatin dosed to achieve an AUC of 7.5. There were no differences in relapse-free survival observed between the 2 groups: 21.7 months vs 22 months in the paclitaxel/cisplatin and paclitaxel/carboplatin regimens, respectively. Again, there was less toxicity in the carboplatin-containing group compared with the cisplatin-containing group.

Although only long-term follow-up could ascertain that the 2 paclitaxel-based combinations with either carboplatin or cisplatin are truly equivalent, the paclitaxel/carboplatin regimen appears to be more attractive because of the ease of administration and the lower toxicity profile. Currently, the combination of paclitaxel (175 mg/m^2, every 3 hours) and carboplatin (AUC 5 or 6) serves as a control arm in most of the prospective randomized phase 3 international trials.

Evaluating Alternative Agents

Recently, the taxane docetaxel has been evaluated as an alternative to paclitaxel in combination with carboplatin. In a phase 3 trial, 1077 patients were randomized to receive carboplatin dosed to achieve an AUC of 5 in combination with either paclitaxel 175 mg/m^2 over 3 hours or docetaxel 75 mg/m^2 over 1 hour.[19] There were no differences observed in the rates of clinical or radiologic responses (62% and 66% in the paclitaxel/carboplatin and docetaxel/carboplatin groups, respectively). After a median follow-up of 23 months, there were no differences in progression-free survival between the 2 arms (15.4 in the paclitaxel combination arm vs 15.1 months in the docetaxel combination arm). No emergent treatment effects were noted in any of the stratified prognostic factors between the 2 arms, such as residual disease, International Federation of Gynecology and Obstetrics (FIGO) stage, age, and performance status.[20] Although this combination is associated with a high rate of hypersensitivity reactions (34%), grade 4 anemia/neutropenia, and neutropenic fever (10%), most patients are able to continue therapy with the use of histamine prophylaxis.[21] In the study, there was significantly less neurotoxicity with docetaxel (11% vs 30%, grade 2 or

greater). Indeed, the follow-up data showed that the paclitaxel combination continued to be significantly more neurotoxic compared with the docetaxel combination up to 14 months after randomization.[20] Thus, the use of the docetaxel/carboplatin combination may be considered for certain subsets of patients where an unacceptable rate of severe neurotoxicity is expected, such as patients with diabetes mellitus.

Monotherapy Vs Combination Therapy

As a follow-up to their earlier study that found that single-agent carboplatin was equivalent to the combination of cyclophosphamide, doxorubicin, and cisplatin as first-line therapy, the International Collaborative Ovarian Neoplasm (ICON) investigators questioned in the ICON3 trial whether carboplatin monotherapy would hold up against the accepted standard of carboplatin/paclitaxel. By contrast, the GOG 132 study investigators took a different approach and examined the use of each element of the accepted standard against the combination in a 3-arm trial of cisplatin vs paclitaxel vs cisplatin/paclitaxel.[22-24] Unfortunately, neither trial serves to settle the question of monotherapy vs combination therapy in the first-line setting.

In the ICON3 trial, 2074 patients with stage I through stage IV ovarian cancer were enrolled; 1421 were randomized to receive carboplatin (dosed to AUC of 6) in combination with paclitaxel (175 mg/m^2 over 3 hours), or to a control of carboplatin (dosed to AUC of 6) alone or the combination of cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2), and cisplatin (50 mg/m^2). After a median follow-up of 51 months, no significant differences were noted in overall survival or progression-free survival between the groups.[23] However, single-agent carboplatin was associated with a more favorable toxicity profile compared with the 2 combination arms, leading the researchers to suggest that a platinum monotherapy might be a viable alternative in the first-line setting.[23]

The GOG 132 study compared cisplatin alone (100 mg/m^2), paclitaxel alone (200 mg/m^2 over 24 hours), and the combination of the 2 agents (paclitaxel 135 mg/m^2 followed by cisplatin 75 mg/m^2) in 614 women with stage III or IV disease.[24] The overall response and progression-free survival rates were higher in the cisplatin-alone and combination arms compared with the paclitaxel-alone arm. However, there were no differences between the combination arm and the cisplatin-alone arm. Overall survival remained similar in all 3 arms. Of note, the combination of cisplatin and paclitaxel was better tolerated than either of the high-dose single-agent arms. Complicating the results of this trial is the fact that about 90% of the patients who were randomized to one of the single-agent arms eventually crossed over to the other single agent. This includes approximately half of the patients who were randomized to the single-agent arms and crossed over to the other single-agent arm prior to clinical progression. Thus, in contrast to the ICON3 trial, the authors of this study concluded that the combination of platinum and paclitaxel should remain the standard therapy.

Intraperitoneal Chemotherapy

To maximize the local cytotoxic effects of the chemotherapy agents while minimizing systemic toxicity, researchers have explored the use of intraperitoneal (IP) chemotherapy for minimal residual tumor after surgery (ie, residual tumor < 1 cm).

The SWOG S9619 trial compared intravenous (IV) cisplatin with IP cisplatin combined with IV cyclophosphamide in 546 patients.[25] A better therapeutic index was achieved when cisplatin was delivered via the IP route compared with the IV route. Patients with stage III minimal residual disease treated in the IP arm experienced better survival (49 and 41 months, respectively), and less severe neutropenia, peripheral neurotoxicity, and hearing loss. The major adverse event reported with the IP administration was an increased rate of abdominal pain. Additional trials were conducted to investigate whether the superiority of the IP route for cisplatin observed with the cyclophosphamide/cisplatin combination could be also demonstrated with the new standard paclitaxel/platinum regimen.

Following on the feasibility data from the SWOG S9619 trial, the GOG 172 trial compared standard IV paclitaxel/cisplatin with a dose-intensified regimen of IV paclitaxel on day 1, IP cisplatin on day 2, and IP paclitaxel on day 8.[26,27] Preliminary results showed that the risk of recurrence was 28% lower compared with the IV-only arm but significantly greater hematologic and nonhematologic toxicities were seen in the IV/IP arm.[27] An earlier study with more mature data demonstrated improved survival, but also recorded significantly greater toxicities, particularly myelosuppression.[28] However, in this trial, patients in the IP arm also received 2 cycles of carboplatin at an AUC of 9.

Whether the acceptance of IP cisplatin becomes sufficiently widespread to be incorporated in the control arm of future studies remains to be seen.[29]

Consolidation Therapy

Because the vast majority of patients relapse after initial therapy, the institution of consolidation or maintenance therapy seemed a promising way to improve survival rates. Unfortunately, attempts to incorporate these strategies into a treatment protocol have not yet shown a clear benefit for this approach.

Preliminary results of a GINECO study group trial suggested that high-dose chemotherapy, consisting of carboplatin 400 mg/m^2 and cyclophosphamide 1500 mg/m^2 daily for 4 days, with peripheral blood stem cell support, was associated with a longer disease-free survival compared with conventional dose maintenance therapy, consisting of carboplatin 300 mg/m^2 and cyclophosphamide 500 mg/m^2 repeated every 4 weeks.[30] The disease-free survival from time of inclusion was 22 months for the high-dose chemotherapy arm and 11 months for the conventional-dose maintenance arm.

However, this trial was conducted in a select group of patients who were younger than 60 years of age and who had a complete response or tumor size of less than 2 cm after second-look surgery. In the absence of overall survival data, high-dose chemotherapy should not be delivered outside of a prospective trial.

The SWOG and GOG recently reported on a trial of paclitaxel consolidation.[31] Patients who had a complete response to initial therapy with carboplatin and paclitaxel were randomized to further treatment with paclitaxel (175 mg/m^2 monthly) for either 3 or 12 months. The progression-free survival was significantly longer in the 12-month arm (28 months) compared with the 3-month arm (21 months), but there was greater toxicity in the 12-month arm. The trial was halted as a result of the improvement in progression-free survival, and it will not be possible to tell if there was an effect on overall survival. Taken together, these data indicate that the role of consolidation therapy yet remains unknown.

Additions to First-line Therapy

Numerous studies have begun examining the addition of a noncross-resistant agent to the platinum/paclitaxel combination as first-line therapy (Table 1). In particular, the anthracyclines, topotecan, and gemcitabine, have all shown promise in this setting.

Epirubicin, a doxorubicin derivative, has been evaluated in association with paclitaxel and carboplatin and compared with the standard paclitaxel/carboplatin regimen in 2 large randomized phase 3 trials. The ACO-GINECO trial enrolled 1247 patients and has shown a higher but nonsignificant overall and complete response rate in the epirubicin (60 mg/m^2) arm. There was no difference in overall survival.[32] Preliminary data from the NSGO-EORTC-NCIC-CTG trial including 888 patients suggest that the addition of higher doses of epirubicin (75 mg/m^2) to the combination of paclitaxel and carboplatin allows patients to achieve a significantly higher clinical complete response rate. Survival data, however, are still incomplete.[33]

Various strategies have been proposed to combine topotecan with paclitaxel and platinum. In the AGO-GINECO trial, 1308 patients have been randomized to receive 6 cycles of the standard paclitaxel/carboplatin regimen followed or not by 4 sequential cycles of topotecan (1.25 mg/m^2/day x 5 days every 3 weeks). Results are awaited in 2004. In the ongoing NCIC-EORTC trial, 4 cycles of topotecan with cisplatin followed by 4 cycles of the paclitaxel/carboplatin regimen will be compared with 8 cycles of the standard latter combination.

The addition of gemcitabine to the paclitaxel/carboplatin regimen is being currently explored by the AGO-GINECO-NSGO intergroup with a similar schedule to that of arm 2 of the GOG trial.

Table 1. Additions to First Line Therapy: Phase 3 Trial Designs

Study Group	Control Arm	Experimental Arm
AGO-GINECO	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1)	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1) Epirubicin 60 mg/m^2 (day 1)
NSGO-EORTC-NCIC CTG	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1)	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1) Epirubicin 75 mg/m^2 (day 1)
AGO-GINECO	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1)	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1) *Then* Topotecan: 1.25 mg/m^2/day (days 1-5)
NCIC-EORTC	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1)	Cisplatin: 50 mg/m^2 (day 5) Topotecan: 0.75 mg/m^2/day (days 1-5) *Then* Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1)
AGO-GINECO-NSGO	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1)	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1) Gemcitabine: 800 mg/m^2/day (days 1, 8)

AUC, area under the curve.

The combination of paclitaxel and carboplatin plus pegylated liposomal doxorubicin, topotecan, or gemcitabine is being evaluated by the GOG 182 study. This study, which will randomize 4000 patients to 1 of 5 arms, is designed to determine the best regimen for first-line treatment of stage III and IV ovarian cancer (Table 2). Recruitment is expected to run through 2004. The experimental arm includes 2 triplets and 2 sets of sequential doublets to add to the third agent.

Table 2. GOG Protocol 182 Trial Design

	Regimen	Dosages
Arm 1 (8 cycles, every	Paclitaxel plus carboplatin (control arm)	Paclitaxel: 175 mg/m^2 (day 1)

21 days)		Carboplatin: AUC = 6 (day 1)
Arm 2 (8 cycles, every 21 days)	Paclitaxel, carboplatin, plus gemcitabine	Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 5 (day 1) Gemcitabine: 800 mg/m$^{2/}$day (days 1, 8)
Arm 3 (8 cycles, every 21 days)	Paclitaxel plus carboplatin, with pegylated liposomal doxorubicin given every other cycle (cycles 1, 3, 5, and 7)	Paclitaxel: 175 mg/m^2 (day 1) pegylated liposomal doxorubicin: 30 mg/m^2 (day 1 of every other cycle) Carboplatin: AUC = 5 (day 1)
Arm 4 (4 cycles each doublet, every 21 days)	Topotecan plus carboplatin, followed by paclitaxel plus carboplatin	Carboplatin: AUC = 5 (day 3) Topotecan: 1.25 mg/m^2/day (days 1-3) *Then* Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 6 (day 1)
Arm 5 (4 cycles each doublet, every 21 days)	Gemcitabine plus carboplatin, followed by paclitaxel plus carboplatin	Carboplatin: AUC = 6 (day 8) Gemcitabine: 1000 mg/m^2/day (days 1, 8) *Then* Paclitaxel: 175 mg/m^2 (day 1) Carboplatin: AUC = 6 (day 1)

AUC, area under the curve.

The inclusion of a gemcitabine combination arm (Arm 2) is based on data from 2 phase 1 studies that evaluated the combination of gemcitabine, paclitaxel, and carboplatin, both of which showed that the combination was well tolerated.[34,35] Patients enrolled in the pegylated liposomal doxorubicin combination arm (Arm 3) will receive the agent with every other cycle of paclitaxel and carboplatin. A phase 1 study previously demonstrated the activity of pegylated liposomal doxorubicin in the first-line setting in combination with carboplatin and paclitaxel at a maximum dose of 30 mg/m^2[36]; the every-other-cycle dosing strategy should maximize efficacy of the triplet while minimizing the hand-foot syndrome (HFS) (also termed palmar plantar erythrodysesthesia) associated with the higher doses of pegylated liposomal doxorubicin.[36]

Patients enrolled in Arm 4 will receive 4 cycles of carboplatin plus topotecan followed by 4 cycles of carboplatin plus paclitaxel, a dosing strategy that has already shown some promise,[37,38] while those enrolled in Arm 5 will receive 4 cycles of carboplatin plus gemcitabine followed by 4 cycles of carboplatin plus paclitaxel.

Until the results of these studies are available, there are insufficient data to support the addition of a third drug to the platinum/paclitaxel combination as first-line therapy for ovarian cancer outside of a clinical trial.

Second-line Therapy

Although first-line therapy in advanced ovarian cancer is associated with high response rates, up to 80% of women will relapse.[39] Currently, there is no widely accepted standard therapy for relapsed disease; however, several agents have been studied, including paclitaxel, oral etoposide, topotecan, gemcitabine, pegylated liposomal doxorubicin, tamoxifen, and platinum-based regimens. Table 3 summarizes some of the agents used in recurrent ovarian cancer along with their respective response rates.

Table 3. Second-Line Chemotherapy for Ovarian Cancer[40-60]

Agent	Overall Response Rate
Etoposide*	6% to 30%
Gemcitabine†	13% to 19%
Paclitaxel§	21% to 48%
Pegylated liposomal doxorubicin‡	20% to 26%
Platinum-based therapy**	21% to 77%††
Tamoxifen‡‡	18%
Topotecan§§	13% to 20.5%***

*Seymour MT, 1994; Rose PG, 1998; Markman M, 1992; Hoskins PJ, 1994. †Lund B, 1994; Shapiro JD, 1996. ‡Muggia FM, 1997; Gordon AN, 2001. §Kohn EC, 1994; McGuire WP, 1989; Einzig AI, 1992; Thigpen JT, 1994; Trimble EL, 1993. **Markman M, 1991; Goldberg JM, 1996; Guastalla JP, 1998. ‡‡Hatch KD, 1991. §§Bookman MA, 1998; Creemers GJ, 1996; Kudelka AP, 1996; ten Bokkel Huinink W, 1997. ††Response rate correlated with platinum-free interval length. ***Majority of patients in these trials had platinum-refractory disease.

The choice of second-line therapy largely depends upon the interval from the completion of platinum-based first-line therapy to relapse. Patients who progress on first-line platinum therapy are said to have platinum-refractory disease; those who relapse within 6 months are considered to have platinum-resistant disease; and those with a relapse-free interval of at least 6 months are said to have potentially platinum-sensitive disease. Thus, in general, patients who have had a disease-free interval of at least 6 months should be considered candidates to receive another platinum-based regimen. Indeed, a number of studies have demonstrated impressive response rates with a second platinum-based regimen in this patient population.

A second-line regimen of 135 mg/m^2 paclitaxel via 24-hour IV infusion followed by 50 mg/m^2 IV cisplatin demonstrated an overall response rate of more than 50% in both platinum-resistant and platinum-sensitive patients; median survival was more than 20 months for responders in both groups.[54] A 3-hour infusion of paclitaxel 175 mg/m^2 followed by a 30-minute carboplatin infusion (AUC 5) demonstrated a 70% overall response rate and a 14-month median survival in platinum-sensitive patients.[55]

The probability of a response to a platinum-based regimen depends upon the length of the interval between first-line platinum therapy and relapse. In a study of 82 patients with relapsed disease, a longer cisplatin-free interval was associated with higher response rates.[53] Patients with a cisplatin-free interval of 5 to 12 months had a 27% response rate, those with a cisplatin-free interval of 13 to 24 months had a 33% response rate, and those with a cisplatin-free interval of more than 24 months had a response rate of 59%. Furthermore, patients who had not received any treatment (including noncisplatin regimens) for more than 24 months from the time of initial cisplatin-based therapy had a response rate of 77%. In those patients

with intervals of > 24 months, there was a greater tendency toward the use of combination therapy. The importance of the therapy-free interval in the outcome has been recently confirmed in a large GINECO study of 583 patients in relapse (Table 4).[61]

Table 4. Response to Chemotherapy, Progression-Free Survival, and Overall Survival Stratified by Therapy-Free Interval and Previous Response to Therapy

N°	TFI (months) Response to first line	Pts (n)	Relapse		
			RR (%)	TTP (days)	OS (days)
1	0-3 Progressive	60	9	90	217
2	0-3 Nonprogressive	91	24	176	375
3	3-12	199	35	174	393
4	12-18	79	52	275	657
5	> 18	154	62	339	957

TFI, therapy-free interval; Pts, patients; RR, response rate; TTP, time to progression; OS; overall survival

Monotherapy Options

As with first-line therapy, the idea of monotherapy offers several potential advantages. It is not necessary to compromise the dose due to the combination, and a single agent is generally less toxic. A second-line regimen of paclitaxel 135 mg/m^2 via 24-hour infusion every 3 weeks demonstrated an objective response rate of 22% and a median survival of 8.8 months.[52] As this agent moved into front-line therapy, there was a need for newer active agents in relapsed disease. Two newer agents have been extensively studied, including in randomized phase 3 trials.

In a phase 3 trial, 226 patients with ovarian cancer who had progressed after 1 platinum-based regimen received 1.5 mg/m^2 topotecan via 30-minute infusion daily for 5 days or 175 mg/m^2 paclitaxel infused over 3 hours every 21 days.[60] Response rates between the groups were similar: platinum-resistant patients demonstrated a response rate of 13.3% with topotecan vs a rate of 6.7% with paclitaxel, while platinum-sensitive patients demonstrated a response rate of 28.8% with topotecan vs a rate of 20% with paclitaxel. Although a significant improvement with topotecan vs paclitaxel was initially noted in the median time to progression (23 weeks vs 14 weeks, respectively; $P = .002$), longer-term follow-up demonstrated no significant difference between the groups.[62]

A follow-up study crossed 100 of the patients from each treatment group to the alternate agent as a third-line therapy for 1 of 3 reasons: failure to respond to the second-line therapy, a demonstrated relapse after an initial response to the second-line therapy, or toxicity.[62] Response rates and median time to progression were similar in both groups, suggesting a lack of cross-resistance between the agents. Of note, platinum-refractory patients did not respond to either agent as third-line therapy.

The question of equivalence between pegylated liposomal doxorubicin monotherapy and paclitaxel or topotecan was also addressed in 2 separate phase 3 trials.[47,63] Of 474 patients with ovarian cancer who had relapsed after first-line, platinum-based therapy, overall, no significant differences were detected between the groups with respect to progression-free survival or objective response rates.[47] However, the subgroup of platinum-sensitive patients demonstrated a significant improvement in median progression-free survival with pegylated liposomal doxorubicin vs topotecan (28.9 weeks vs 23.3 weeks, respectively; $P = .037$). A significant difference in overall survival was also noted in this group, with a median survival of

108 weeks noted in the platinum-sensitive pegylated liposomal doxorubicin group vs 71.1 weeks in the platinum-sensitive topotecan group ($P = .008$). As the authors noted, the improvement in response rates and survival outcomes in platinum-sensitive patients is consistent with observations in other studies with other agents.[60]

A phase 3 trial comparing 50 mg/m^2 pegylated liposomal doxorubicin via 1-hour infusion every 4 weeks with 175 mg/m^2 paclitaxel via 3-hour infusion every 3 weeks was conducted in 214 patients with recurrent ovarian cancer following first-line platinum therapy that did not contain paclitaxel.[63] Preliminary results demonstrated equivalent survival rates between the groups: progression-free survival with pegylated liposomal doxorubicin was 21.7 weeks vs 22.4 weeks with paclitaxel, while median survival with pegylated liposomal doxorubicin was 45.7 weeks vs 56.1 weeks with paclitaxel. The overall response rate was also similar between the groups, with 17.8% of pegylated liposomal doxorubicin patients and 22.4% of paclitaxel patients demonstrating a response to the second-line therapy. In contrast with the topotecan trial, no significant differences were noted when the data were analyzed according to platinum sensitivity.

Given the significant survival advantage with pegylated liposomal doxorubicin over topotecan in patients with platinum-sensitive disease and its equivalence to topotecan in patients with platinum-resistant disease, pegylated liposomal doxorubicin emerges as an important monotherapy option for patients with recurrent ovarian cancer. (This would be particularly true since patients receive paclitaxel in the first-line setting.) Indeed, the National Institute for Clinical Excellence in the United Kingdom has identified single-agent pegylated liposomal doxorubicin as the agent of choice for patients with recurrent or relapsed ovarian cancer.

Combination Therapy Options

To date, there are no randomized trials that have demonstrated a benefit of combination therapy over monotherapy in the second-line setting. ICON4 trial, a randomized phase 3 trial that began recruiting in 1996, was designed to compare the effectiveness of platinum chemotherapy with or without paclitaxel in the treatment of patients with relapsed ovarian cancer.

Patients randomized to Arm 1 received cisplatin or carboplatin alone; patients in Arm 2 received paclitaxel intravenously over 3 hours followed by either carboplatin or cisplatin. Treatment was administered every 3 weeks for up to 6 courses in the absence of unacceptable toxicity. Follow-up was scheduled at 6 months, every 3 months for 2 years, every 6 months for 3 years, and then annually thereafter. Patients were eligible if they demonstrated ovarian epithelial cancer or serous peritoneal carcinoma that relapsed after prior chemotherapy, with a progression-free interval (from end of last treatment) of at least 6 months. A total of 800 patients were recruited; results are expected to be presented in 2003.

The question of monotherapy vs combination therapy in recurrent ovarian cancer is also being explored in a number of other trials. For example, trials evaluating the combinations of pegylated liposomal doxorubicin plus carboplatin, gemcitabine plus carboplatin, and pegylated liposomal doxorubicin plus gemcitabine are currently under way by the Southwest Oncology Group. Data from all of these trials may help to identify a combination that can improve upon current single-agent treatments.

Quality-of-Life Considerations

When selecting a therapy, it is important to remember that the goal of second-line therapy is palliation; therefore, improving or maintaining the patient's quality of life must be a priority.

Because each of the active agents in recurrent ovarian cancer has a unique mechanism of action, the toxicity profiles are often nonoverlapping. It is therefore easier to identify more favorable or less favorable toxicities based on patient preference and/or available supportive therapies. For example, in trials with both pegylated liposomal doxorubicin and topotecan,

paclitaxel was associated with a greater incidence of alopecia, which can confer negative psychological effects on patients and which cannot be reversed until after therapy has been discontinued.[60,63] Similarly, topotecan was associated with a greater incidence of myelosuppression when compared with pegylated liposomal doxorubicin, resulting in greater use of hematopoietic growth factors and dosing modifications.[47] By contrast, the most common adverse event associated with pegylated liposomal doxorubicin is HFS, which can be managed sufficiently during therapy to minimize the need for dose modifications and severe reactions.[47] Indeed, although 49% patients in the pegylated liposomal doxorubicin vs topotecan trial experienced HFS, overall, there were only 17% grade 4 toxicities in the pegylated liposomal doxorubicin arm vs 71% grade 4 toxicities in the topotecan arm (which were largely hematologic in nature).

Patient compliance and preference has also emerged as an important consideration in selecting a therapeutic option. Because the 3 proven active monotherapy agents are all administered via IV infusion, the duration of infusion and the frequency of administration can serve as points of differentiation. For example, although the duration of topotecan infusion is only 30 minutes, the 5-times-weekly regimen might prove difficult for some patients. Overall, particularly when the primary goal of therapy is palliation, taking into account patient preference and compliance is of paramount importance.

The Role of Surgical Intervention in Medical Management

The value of debulking surgery in the management of advanced ovarian cancer has been demonstrated by a randomized EORTC study, which showed a benefit in both progression-free and overall survival with debulking surgery.[64] Patients with residual disease after primary surgery of at least 1 cm were treated with 3 cycles of cisplatin and cyclophosphamide. Those who had a complete or partial response or stable disease were then randomized to debulking surgery or to no surgery, followed by 3 more cycles of cisplatin and cyclophosphamide. The median survival was 6 months longer in the group that underwent debulking surgery vs the group that did not (26 months vs 20 months).

This trial raised the question of the benefit of performing an intermediate debulking surgery in addition to the initial surgical procedure. Recently, the GOG reported the results of a study with a schedule similar to that of the EORTC study, but in contrast, initial surgery was performed by surgeons trained in gynecologic oncology and patients were treated with a paclitaxel/platinum combination instead of the less effective cyclophosphamide/platinum regimen. No benefit from a second intermediate surgery was found, suggesting that a unique surgical procedure performed by a trained surgeon could be sufficient in the treatment of advanced ovarian cancer.[65] The time when surgery should optimally be performed remains open to question.

A small Italian study examined neoadjuvant chemotherapy in 34 women with unresectable stage IV ovarian cancer.[66] Patients enrolled early in the course of the trial were treated with 4 cycles of carboplatin, cyclophosphamide, and epirubicin; those enrolled after October 1996 were treated with 4 cycles of carboplatin and paclitaxel. Patients then underwent surgery followed by 2 more cycles of chemotherapy. The overall response rate was 82% and the 1-year survival rate was 94%. The median time to progression was 16.45 months. A phase 3 trial to establish the role of neoadjuvant chemotherapy in the treatment of metastatic ovarian cancer is currently being conducted by the EORTC.

Future Therapies

Despite the progress made in refining the chemotherapy regimens used in the treatment of ovarian cancer, the majority of patients with this disease will relapse and eventually die of their disease. Although a number of newer chemotherapeutic agents are being developed, much of the focus of research efforts has shifted toward novel agents, including immunologic agents (such as vaccines) and targeted agents toward specific molecular pathways.

Immunotherapy

One area of interest is in the development of monoclonal antibodies directed against CA-125. Oregovomab is a murine monoclonal antibody with high affinity to CA-125 that has been studied in patients with ovarian cancer. In a randomized, placebo-controlled trial, a total of 325 patients with stage III and IV disease who had responded to initial therapy with surgery and chemotherapy were randomized to receive adjuvant oregovomab or placebo.[67] Immunologic responses as demonstrated by the presence of anti-idiotypic antibodies or human antimouse antibodies were seen in 55% of patients in early data. Of note, patients who developed immunologic responses had a 2-fold longer median time to relapse compared with those who did not have immune responses.

Another approach is to vaccinate patients with an anti-idiotype CA-125 monoclonal antibody, which has been demonstrated to generate an immunologic anti-CA-125 response in 60% of ovarian cancer patients whose outcome is significantly better than that of nonresponder patients.[68]

IM862 is a synthetic version of a naturally occurring peptide (L-glutamyl-L-tryptophan) that stimulates the immune system and inhibits angiogenesis. The drug has a very small molecular weight, making it absorbable through mucous membranes and allowing for intranasal administration. Doses from 5 mg every other day to 120 mg per day studied in a phase 1/2 trial were well tolerated.[69] In this heavily pretreated population of 74 patients, 1 patient had an objective response and 26 patients had stable disease. The lack of toxicity makes this an interesting agent for a possible third agent as part of a triplet.

Molecularly Targeted Therapy

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib are currently being studied in ovarian cancer. These agents are attractive because they are administered orally and are associated with minimal adverse effects. Preclinical data suggest that gefitinib may act synergistically with chemotherapy in ovarian tumors that have high expression of the epidermal growth factor receptor.[70] The GOG is currently evaluating gefitinib in a phase 2 study of patients with recurrent ovarian cancer.

Erlotinib has already been evaluated in a phase 2 study, the preliminary results of which have already been released.[71] Thirty-four patients with relapsed or refractory disease with EGFR-overexpressing tumors were treated with daily erlotinib. Three patients had partial responses and 14 patients (42%) had stable disease. The NCIC is currently conducting a phase 2 study of erlotinib in combination with carboplatin in relapsed ovarian cancer.

Vascular endothelial growth factor (VEGF) overexpression in ovarian cancer cells is thought to be an important factor in tumor angiogenesis and biologic aggressiveness. A number of agents are being developed to target VEGF in the treatment of various solid tumors. Bevacizumab is a recombinant monoclonal antibody to VEGF that has been studied in a number of solid tumors including renal cell, colorectal, and lung cancer. The GOG is currently conducting a phase 2 trial of bevacizumab in the treatment of persistent or recurrent ovarian cancer.

Other novel agents being evaluated in the treatment of ovarian cancer include the proteasome inhibitor PS-341 (bortezomib), the matrix metalloproteinase inhibitor BAY 12-9566, and the small molecule SU6668, which inhibits the Flk-1/KDR, platelet-derived growth factor, and fibroblast growth factor receptors.

Conclusions

The combination of paclitaxel with either cisplatin or carboplatin remains the standard first-line chemotherapy for the treatment of ovarian cancer. However, although the majority of women respond to initial therapy, most eventually relapse. Therefore, research efforts are focusing on

improving the response to chemotherapy by, generally, adding a third agent to front-line therapy to try to prolong disease-free and progression-free survival, and by better defining the optimal therapeutic strategy for recurrent disease.

Nevertheless, even these strategies may prove insufficiently effective, and continued study of novel therapies designed to enhance the immune response to ovarian cancer or to target specific molecular mechanisms of tumor growth may ultimately be the only hope. We hope the next decade will yield significant progress in the treatment of this deadly disease.

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