MANAGEMENT OF RELAPSED/REFRACTORY EPITHELIAL OVARIAN CANCER: CURRENT STANDARDS AND NOVEL APPROACHES

Hao Lin, Chan-Chao Changchien*

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

SUMMARY

Approximately 60% to 70% of epithelial ovarian cancers are diagnosed at an advanced stage. Treatment of advanced disease involves cytoreductive surgery followed by systemic treatment with paclitaxel and platinum. Overall response rates are high, ranging from 70–80%; however, 70–80% of responders will relapse and require further systemic chemotherapy. Patients who experience disease relapse with platinum-free interval of less than 6 months are considered as platinum-refractory/resistant individuals. In this clinical setting, agents with non-cross-resistance to first-line therapy and favorable toxicity profiles are usually chosen. In the management of relapsed patients with platinum-free interval over 6 months, the generally accepted recommendation is retreatment with a platinum plus paclitaxel combination. In general, 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. A number of currently available and novel investigating agents in recurrent epithelial ovarian cancer will be reviewed in this context. [*Taiwan J Obstet Gynecol* 2007;46(4):379–388]

Key Word: relapsed ovarian cancer

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer among women. An estimated 600 new cases are diagnosed in Taiwan annually, and approximately 350 women will die from the disease [1]. The high mortality rate of this disease may be partly explained by the difficulty in early diagnosis and lack of a reliable screen test. Current management for advanced EOC is cytoreductive surgery followed by combination chemotherapy, usually a platinum-based (mostly carboplatin plus paclitaxel) regimen. With the combination of surgery and chemotherapy, the median survival of patients with advanced disease is around 44 months [2]. Despite this progress in primary treatment of EOC in the past decade, most patients will relapse, highlighting the need for effective and well-tolerated regimens for recurrent disease. To date, there is no curative treatment for these patients. The main goals of second-line treatments are to control symptoms and maintain quality of life, and if possible, to improve progression-free survival (PFS) and overall survival (OS).

It has become clear over the last decade that the likelihood of response to chemotherapy at the time of recurrence is directly proportional to the time between completion of first-line chemotherapy and the confirmation of recurrent disease. The treatment-free or platinum-free interval has been shown to strongly predict the chance of response to a second-line chemotherapy. Based on the data of Markman and Hoskins [3], patients with recurrent disease are divided into two subgroups: those with platinum-refractory/resistant disease and those with platinum-sensitive disease. Platinum-refractory/resistant

Correspondence to: Dr Chan-Chao Changchien, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital–Kaohsiung Medical Center, 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung, Taiwan.
E-mail: chanchao@adm.cgmh.org.tw
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disease is characterized by no response to prior platinum chemotherapy or progression within the first 6 months after the end of primary therapy. Secondary non-cross-resistant chemotherapies or biologic therapies should be considered. The median PFS in this group of patients is around 22 weeks and the median OS about 40 weeks. Platinum-sensitive disease is characterized by a response to prior platinum chemotherapy (at least partial response) and a progression-free interval of at least 6 months. This group shows the best responses to retreatment with a platinum-containing regimen. In general, the longer the platinum-free interval, the greater the expectation of durable response to retreatment. The median PFS and OS are around 40 and 60 weeks, respectively. Therefore, before initiating second-line chemotherapy, it is important to determine the interval between the completion of therapy with cisplatin or carboplatin and the development of recurrent disease.

Timing of Treatment

The most debated question remains the timing of treatment in patients with an asymptomatic increase of the tumor marker CA125, without detectable lesions on clinical or radiologic examinations. Although rising CA125 in asymptomatic patients is highly predictive of clinical recurrence within 4–6 months [4,5], whether treatment should be delayed until appearance of symptoms or initiated solely on the increase in CA125 level to prevent symptom occurrence remains controversial. However, this is being addressed in an on-going randomized trial. The kinetics of the CA125 increase, as well as the patient's inclination for treatment, should help with the decision.

Current Treatment Options for Platinum-refractory/resistant EOC

As implied by the name, for patients with platinum-refractory/resistant disease, the standard of care is non-platinum chemotherapy or biologic therapy. The main goals are to alleviate symptoms, maintain quality of life, delay tumor progression, and prolong survival. Various agents with moderate activity are available for these patients. Currently, there are no data supporting a combination therapy for this group of patients.

Pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin (PLD) is a stealth liposomal form of doxorubicin that differs from conventional doxorubicin in its long plasma half-life, extended circulation time, and distribution throughout the body. It has been approved by the United States' Food and Drug Administration (FDA) in 2005 for treatment of relapsed EOC patients. A response rate of 18–25% has been shown in patients with both platinum- and/or paclitaxel-refractory/resistant EOC receiving single-agent PLD at a dose of 50 mg/m^2 every 4 weeks in two previous phase II studies [6,7]. A similar response rate of 23–28% has also been reported in Taiwanese populations but with a lower dose at 40–45 mg/m^2 every 4 weeks [8,9]. The median PFS and OS were about 5 months and 12 months, respectively. Only 12% and 20% of patients developed grade 3–4 neutropenia and palmar-plantar erythrodysesthesia, respectively. Other grade 3–4 toxicities were very rare. Several advantages were observed from previous studies of using PLD, such as fewer dose modifications, less frequent treatment for low blood counts, and a lower total cost per patient. In addition, PLD improved cardiac safety when compared with free doxorubicin. Based on the survival and side-effect advantages and the once-monthly dosing schedule, PLD is considered to be the first choice for non-platinum chemotherapy for relapsed ovarian cancer.

Topotecan

Topotecan, a topoisomerase I inhibitor, has also been approved by the FDA for the treatment of relapsed EOC. It has been extensively evaluated as a single agent in patients with platinum-refractory/resistant EOC. In phase II studies of topotecan that was administered intravenously on days 1 to 5 at a dose of 1.5 mg/m^2/day of a 21-day cycle, objective response rates ranging from 6% to 17.8% have been reported [10–12]. The major toxicities were leukocytopenia and neutropenia, which were grade 3–4 in almost 60–70% of patients. In a phase III study comparing topotecan and PLD in the treatment of platinum-refractory/resistant EOC [13], the response rates (6.4% *vs.* 12.3%), PFS (13.6 weeks *vs.* 9.1 weeks), and OS (41.3 weeks *vs.* 35.6 weeks) did not differ significantly. However, grade 3–4 neutropenia was observed in almost 80% of patients in the topotecan arm but only 10% in the PLD arm. Owing to the substantial myelosuppression following administration, alternative dosing schedules such as once weekly have been evaluated in an attempt to minimize toxicity while maintaining antitumor activity. In recent phase II studies using topotecan 4 mg/m^2 on days 1, 8, 15 of a 28-day cycle in treating relapsed EOC, objective response rates of 14–23% were reported, while only 10–30% of patients experienced grade 3–4 neutropenia [14,15]. Based on these data, weekly topotecan may be an appropriate treatment option for patients with recurrent ovarian cancer, especially heavily pretreated patients who might

require dosing schedules with improved tolerability. A randomized phase II trial directly evaluating topotecan administered daily for 5 days every 3 weeks versus weekly topotecan with one week off is now ongoing (Gynecologic Oncology Group-146Q trial).

Paclitaxel

For more than 15 years, platinum-based combination chemotherapy has been the cornerstone of frontline chemotherapy for ovarian cancer. With the development of paclitaxel in the 1990s, platinum plus paclitaxel has become the standard treatment all over the world. Fortunately, the mechanisms of acquired drug resistance are different between paclitaxel and platinum, and not all patients with platinum-resistant disease are resistant to paclitaxel, even if paclitaxel was included in their frontline treatment program. Furthermore, the spectrum of toxicity varies widely depending on the schedule of drug administration, which raises a possibility that alternative schedules may increase the likelihood of response in patients with refractory/resistant disease. In a phase I study, paclitaxel administered intravenously as a 1-hour infusion every week at a dose of 80 mg/m^2 did not result in cumulative myelosuppression while maintaining activity [16]. Since then, weekly administration at a dose of 80 mg/m^2 has been extensively investigated by several groups with reports suggesting that 10–20% of patients will achieve an objective response [17–22]. Serious adverse events were relatively uncommon with grade 3–4 neurotoxicity at around 5–15%, while grade 3–4 hematologic toxicities were rarely encountered. Based on these results, weekly paclitaxel is a reasonable treatment option for patients with refractory/resistant ovarian cancer, balancing efficacy, toxicity, and quality of life benefits.

Oral etoposide

The "standard" 3-day intravenous etoposide regimen, originally developed for lung cancer treatment, has limited activity in ovarian cancer. However, several studies reported that a prolonged 21-day low-dose oral etoposide regimen (50 mg/m^2/day) resulted in a 25% objective response rate in the second-line setting in patients with ovarian cancer [23,24]. The major toxicity of oral etoposide is bone marrow suppression, with grade 3–4 neutropenia occurring in about 45% of patients. Oral etoposide has the clear advantage of convenient home administration, requiring, however, weekly evaluation of blood counts.

Gemcitabine

Gemcitabine, approved by the FDA for treatment of pancreatic cancer, has been demonstrated to be an active second-line agent in relapsed ovarian cancer. Gemcitabine is generally administered on a weekly schedule for 3 consecutive weeks, followed by a 1-week treatment break using a dose of 800 to 1,100 mg/m^2/week as a 30-minute infusion. Several phase II trials have revealed a 15% to 20% objective response rate in this clinical setting [25–28]. Gemcitabine has been reported to be well tolerated, with major side effects being grade 3–4 neutropenia in 30–50% of patients.

Docetaxel

Docetaxel is an inhibitor of microtubule depolymerization and has demonstrated activity in both platinum- and paclitaxel-resistant EOC but with significant hematologic toxicity. In phase II studies of docetaxel that was administered intravenously as 1-hour infusion at a dose of 75–100 mg/m^2 every 3 weeks, objective response rates ranging from 10% to 22% have been reported [29,30]. The principal adverse effect of grade 3–4 neutropenia occurred in 50–75% of patients. Several investigators have evaluated that a lower dose regimen (30 or 40 mg/m^2) administered weekly might result in a similar response rate with reduced toxicity. The results were promising with response rates at 7–19% and toxicity being grade 3 neutropenia in only 4% of patients [31,32].

Novel Therapeutic Approaches for Platinum-refractory/resistant EOC

Bevacizumab (Avastin)

Vascular endothelial growth factor overexpression in ovarian cancer cells is thought to be an important factor in tumor angiogenesis and biologic aggressiveness. Bevacizumab is a humanized recombinant monoclonal antibody that blocks cancer cells from secreting vascular endothelial growth factor and is hence called an anti-angiogenic agent. Bevacizumab has been approved by the FDA for patients with colorectal cancer and metastatic breast cancer. Several prospective phase II trials have also reported significant activity in platinum-refractory/resistant ovarian cancer. In those reports, bevacizumab was administered intravenously at a dose of 15 mg/kg every 3 weeks, and an objective response rate of 16–18% was observed [33,34]. Common toxicities associated with bevacizumab included hypertension, proteinuria, and wound healing complications and did not differ from other phase II and III studies performed in non-gynecologic cancers. Recently, bowel perforations associated with bevacizumab have gained significant attention, because they seem to be more common in ovarian cancer than other solid tumors.

In a review article, the overall risk of bowel perforations from bevacizumab therapy was 5.4% [35]. Although the risk is not so high, it is life-threatening. The pathophysiologic mechanism by which bowel perforations occur is unknown, but it is thought that when bevacizumab destroys the cancer cells in the bowel serosa, it leaves perforations in the bowel. Further studies are necessary to continue to assess the safety of bevacizumab.

Trabectedin (ET-743, Yondelis)

Trabectedin, a novel marine-derived chemotherapeutic agent, was discovered in the colonial tunicate *Ecteinascidia turbinata* and is now produced synthetically. Trabectedin has a unique mechanism of action. It binds to the minor groove of the DNA and interferes with the cell division and genetic transcription processes and the DNA repair machinery. The recommended dosing schedules of trabectedin varies, ranging from 1.2–1.65 mg/m^2 given as a 1-, 3-, 24- or 72-hour intravenous infusion every 3 weeks, with the most prevalent dose-limiting toxicities being hematologic [36–38]. In a phase II trial with patients with platinum-refractory/resistant EOC, the objective response rate was 7% (43% in platinum-sensitive disease) at a dose of 1.3 mg/m^2 given as a 3-hour infusion every 3 weeks. The predominant toxicities were grade 3–4 neutropenia and thrombocytopenia in 41% and 8% of the patients, respectively [39]. Additional studies to establish empirical dosing guidelines as a single agent or in combination regimens may be necessary to improve the efficacy and safety of the drug.

Epothilones

The epothilones are a novel class of non-taxane microtubule-stabilizing agents obtained from the fermentation of the cellulose-degrading myxobacteria, *Sorangium cellulosum*. Similar to paclitaxel and other taxanes, the epothilones block cells in mitosis, resulting in cell death [40]. Preclinical studies have shown that the epothilones are more potent than the taxanes and are active in some taxane-resistant models [41]. The major components of the fermentation process are epothilones A and B, with epothilones C and D found in smaller amounts. Preclinical studies have shown that epothilone B (patupilone) is the most active form, exhibiting significantly higher antitumor activity than paclitaxel and docetaxel [42]. In a phase I/II trial with patients with relapsed/refractory ovarian cancer, patupilone at a dose of 10.5 mg/m^2 administered intravenously over 10–20 minutes every 3 weeks was safe and well tolerated with an objective response rate of 16%. The principal adverse effect of grade 3–4 diarrhea and fatigue occurred in 17% and 14% of the patients, respectively [43]. A randomized, parallel-group, multicenter phase III trial of patupilone (10.5 mg/m^2 every 3 weeks) versus PLD (50 mg/m^2 every 4 weeks) in platinum-refractory/resistant EOC is now ongoing [44]. The main objectives are to access tumor response, PFS, and time to progression compared with conventional PLD. Results will be reported in the near future.

TLK286 (Telcyta): a cytotoxic prodrug

TLK286 was designed to exploit the overexpression of glutathione S-transferase P1-1 (GST P1-1), an enzyme overexpressed in many human cancer cells. High levels of GST P1-1 are associated with a poor prognosis and resistance to certain chemotherapeutics. Preclinical studies suggest that the activation of TLK286 occurs when GST P1-1 splits TLK286 into two active fragments: a glutathione analog fragment and an active cytotoxic fragment [45]. The cytotoxic fragment reacts with important cell components, including RNA, DNA and proteins, leading to cell death (Figure 1). The glutathione analog fragment of TLK286 may remain bound to GST P1-1, which may limit the ability of GST P1-1 to inactivate other cancer drugs, thus reversing drug sensitivity. The results of preclinical studies provide a rationale for its use in the clinical management of platinum-resistant ovarian cancer [46]. In a phase II trial with patients with platinum-refractory/resistant EOC, an objective response rate of 15% (50% with stable disease) at a dose of 1,000 mg/m^2 given as a 30-minute infusion every 3 weeks was observed [47]. There were no

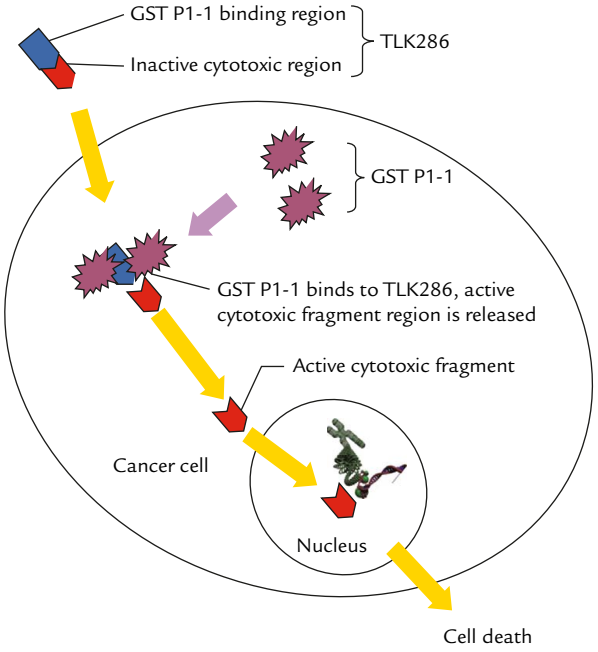

Figure 1. TLK286 is activated by the enzyme glutathione S-transferase (GST) P1-1. Once activated, the cytotoxic fragment is released, inducing apoptosis.

grade 4 toxicities. Grade 3 toxicities were infrequent, and no cumulative toxicities were seen in this population. Later, phase I/II studies regarding outcomes in platinum-refractory patients with TLK286 in combination with carboplatin (TLK286 500 mg/m^2, carboplatin at an area under curve [AUC] 5) or PLD (TLK286 960 mg/m^2, PLD 50 mg/m^2) were presented [48,49]. The combination showed enhanced efficacy with a response rate of 46% to 56% being observed. Grade 3 neutropenia was reported in 62% of patients receiving the TLK286–carboplatin combination. Because of the promising results, the ASSIST-Ovarian (ASsessment of Survival In Solid Tumors) phase III clinical trials are currently being conducted to compare TLK286 (either alone or in combination with carboplatin or PLD) with drugs already approved for the treatment of recurrent ovarian cancer (PLD and topotecan) [50]. The results will be reported in the near future.

Phenoxodiol

Phenoxodiol, an isoflavone analog, belongs to a new class of anticancer drugs known as multiple signal transduction regulators. The drug regulates signal pathways in cancer cells. It works selectively on cancer cells and induces cancer cell death through inhibition of anti-apoptotic proteins, including X-linked inhibitor of apoptosis protein (XIAP) [51]. XIAP was shown to be overexpressed in chemo-resistant cells, and phenoxodiol may serve as a chemosensitizer by interfering with XIAP activity [52,53]. A phase I study showed that phenoxodiol at a dose of 30 mg/kg/day given by intravenous infusion continuously for 7 days on 14-day cycles was well tolerated [54]. Phenoxodiol is now being tested for women with refractory/resistant ovarian cancer as a chemosensitizer (OVATURE trial). This is a multicenter, randomized, double-blind, phase III efficacy study comparing phenoxodiol in combination with carboplatin versus carboplatin with placebo. The study has started since October 2006 and is expected to recruit 470 patients [55].

Others targeted agents

Other novel targeted agents being investigated in the treatment of ovarian cancer include anti-CA125 antibody (oregovomab), anti-epidermal growth factor receptor (EGFR) antibody (cetuximab), EGFR tyrosine kinase inhibitor (gefitinib), anti-HER2/*neu* antibody (pertuzumab), and proteasome inhibitor (bortezomib). All these agents show clinical activity and present a different safety profile from that of conventional chemotherapeutic agents. Combination strategies with platinum/taxane-based therapy are being evaluated for some of these inhibitors/antibodies in phase II/III trials. The response rate to treatment with various single agents in patients with EOC in refractory/resistant relapse are summarized in Table 1.

Current Treatment Options for Platinum-sensitive EOC

Patients in this clinical setting are frequently considered candidates for retreatment with regimens, similar to those previously received in the frontline therapy, including cisplatin, carboplatin or paclitaxel. Current studies have shown that platinum combination chemotherapy

Table 1. Response rate to treatment with single agent in patients with platinum-refractory/resistant relapse

Agent	References	Principal grade 3–4 toxicity	ORR (%)
PLD	6, 7, 8, 9, 13	Neutropenia, 12%; PPE, 20%	18–28
Topotecan (q3w)	10, 11, 12, 13	Neutropenia, 70–80%	6–18
Topotecan (qw)	14, 15	Neutropenia, 10–30%	14–23
Paclitaxel (qw)	17, 18, 19, 20, 21, 22	Neuropathy, 5–15%	10–20
Oral etoposide	23, 24	Neutropenia, 45%	25
Gemcitabine	25, 26, 27, 28	Neutropenia, 30–50%	15–20
Docetaxel (q3w)	29, 30	Neutropenia, 50–75%	10–22
Docetaxel (qw)	31, 32	Neutropenia, 4% (grade 3)	7–19
Bevacizumab	33, 34, 35	Bowel perforation, 5.4%	16–18
Trabectedin	39	Neutropenia, 41%; thrombocytopenia, 8%	7
Epothilones (patupilone)	43	Diarrhea, 17%; fatigue, 14%	16
TLK286	47	Rare	15
TLK286 + carboplatin	48	Neutropenia, 62%; thrombocytopenia, 37%	63
TLK286 + PLD	49	Neutropenia, 12%; fatigue, 6%	46
Phenoxodiol	54	NA	NA

ORR = overall response rate; PLD = pegylated liposomal doxorubicin; PPE = palmar/planter erythrodysesthesia; q3w = every 3 weeks; qw = every week; NA = no phase II trial available.

achieves superior outcomes with regard to survival or quality of life compared with the use of single agents. In selected patients, secondary cytoreductive surgery before initiation of chemotherapy may have some role in survival benefit.

Secondary cytoreductive surgery

Until today, only few publications have focused on selection criteria for secondary cytoreductive surgery in recurrent ovarian cancer. Based on available data, secondary cytoreductive surgery is best considered only for those patients who have all of the following characteristics: (1) disease-free interval of at least over 12 to 18 months, (2) response to frontline chemotherapy, (3) younger age, (4) good performance status, and (5) potentially can be rendered free of all gross residual disease [56,57]. However, it is difficult to preoperatively predict whether it will be possible to achieve complete tumor resection. In a retrospective analysis, factors associated with successful surgery include no residual disease after initial surgery, good performance status, absence of ascites, and no evidence of peritoneal carcinomatosis. A complete resection was shown to be possible in 81% of patients when all these criteria were present [58].

Platinum plus paclitaxel

Results of the International Collaborative Ovarian Neoplasm 4 (ICON4)/AGO-OVAR 2.2) trial suggest that combination treatment with a platinum–paclitaxel doublet shows a survival benefit over single-agent platinum in patients with relapsed platinum-sensitive ovarian cancer [59]. This randomized trial compared a minimum of six cycles of single-agent platinum chemotherapy versus platinum–paclitaxel doublet in 802 patients with relapsed ovarian cancer. A treatment-free interval of more than 6 months was required. In this setting, platinum–paclitaxel doublet therapy yielded a response rate (66%) that was superior to single-agent platinum (54%). At a median follow-up of 42 months, the hazard ratio for PFS was 0.76 (12 *vs.* 9 months; $p = 0.0004$), favoring platinum–paclitaxel doublet. The hazard ratio for OS was 0.82 ($p = 0.0023$), corresponding to an absolute difference in 2-year survival of 7% (57% *vs.* 50%) and median survival of 5 months (29 *vs.* 24 months), favoring the platinum–paclitaxel doublet. However, the improved survival was accompanied by increased grade 3–4 neurologic toxicity (20% *vs.* 1%) and alopecia (86% *vs.* 25%).

Carboplatin plus gemcitabine

In view of the high incidence of neurotoxicity and alopecia which should be avoided in patients in relapse, the Gynecologic Cancer InterGroup (GCIG) trial AGO-OVAR 2.5 randomized 356 patients with platinum-sensitive disease to carboplatin–gemcitabine doublet (carboplatin: AUC 4, day 1; gemcitabine: 1,000 mg/m^2, days 1 and 8) versus single-agent carboplatin (AUC 5) every 3 weeks [60]. A significantly higher overall response rate was observed in the carboplatin–gemcitabine doublet group (47.2% *vs.* 30.9%; $p = 0.0016$). Also, the combination regimen produced a significantly longer PFS compared with the single-agent carboplatin control arm (8.6 *vs.* 5.8 months) with a hazard ratio of 0.72 (95% confidence interval, 0.50–0.90 months; $p = 0.003$). The trial was not powered for OS. Alopecia and neurotoxicity rates were low in both arms, but grade 3–4 hematologic toxicities were significantly more common with combination therapy (78.3% *vs.* 24.7%). Based on the results of the above two randomized trials, there is enough evidence to conclude that platinum-based doublet chemotherapy is superior to single-agent carboplatin in patients with recurrent platinum-sensitive ovarian cancer; however, there is still a need for carboplatin-based combinations, which may offer the best outcome while minimizing toxicity and preserving quality of life.

Carboplatin plus PLD

A more recent phase II study conducted by Groupe des Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire (GINECO) also has shown activity for other combination regimens, including the combination of carboplatin (AUC 5) and PLD (30 mg/m^2) administered every 4 weeks [61]. The overall response rate was 63%, with 38% of patients demonstrating complete response. Although the population enrolled in this large phase II trial of 105 patients was slightly different from those enrolled in ICON4/AGO-OVAR 2.2 and GCIG/AGO-OVAR 2.5, PFS and OS were similar for carboplatin plus PLD and platinum plus paclitaxel. Hematologic and non-hematologic toxicities were low, with less than 15% of patients experiencing grade 2 alopecia, grade 2 or 3 infection, mucositis, hand–foot syndrome or neuropathy. The data suggest that combination therapy with carboplatin and PLD may be a feasible alternative to platinum–paclitaxel doublet therapy in relapsed ovarian cancer patients with platinum-sensitive disease. These encouraging results have prompted the GCIG to launch a randomized trial comparing the efficacy and tolerability of carboplatin (AUC 5) combined with either PLD (30 mg/m^2) or paclitaxel (175 mg/m^2) in patients with ovarian cancer in late relapse (CALYPSO trial, AGO-OVAR 2.9). The study is ongoing and is expected to recruit 864 patients. The results of the above three major trials are summarized in Table 2.

Table 2. Comparison of efficacies and toxicities of platinum doublet regimens for patients with platinum-sensitive relapse

	Platinum/paclitaxel (ICON4/AGO-OVAR 2.2 [59])	Carboplatin/gemcitabine (GCIG/AGO-OVAR 2.5 [60])	Carboplatin/PLD (GINECO [61])
Number of patients	392	175	105
Platinum-free interval (%)			
6–12 months	24	40	47
>12 months	76	60	53
Efficacy			
Overall response rate (%)	66	47	63
Median PFS (mo)	12	8.6	9.4
Median OS (mo)	26	18	32
Adverse events (%)*			
Neutropenia, grade 3–4	29†	70.3	51
Neurotoxicity, ≥ grade 2	20	6.3	7
Alopecia, ≥ grade 2	86	14.3	12
Mucositis, ≥ grade 2	7	–	12
PPE, ≥ grade 2	0	0	11

**Based on National Cancer Institute Common Toxicity Criteria version 2.0 and later; †hematologic toxic effect leading to treatment modification or interruption reported. PLD = pegylated liposomal doxorubicin; PFS = progressive-free survival; OS = overall survival; PPE = palmar/planter erythrodysesthesia.*

Non-platinum single agent

As discussed previously, current treatment options for patients with platinum-sensitive ovarian cancer include retreatment with a platinum doublet combination. Although a survival benefit has been demonstrated with combined therapy, 7–10% of patients are unable to tolerate retreatment because of neuropathy, myelosuppression or hypersensitivity [62]. In these patients, non-platinum agent such as PLD should be the treatment of choice, as it has clearly shown to have a survival advantage compared with topotecan in a phase III clinical trial [13]. In this phase III clinical trial comparing PLD with topotecan in 220 women with platinum-sensitive relapsed EOC, the response rates in both arms were similar (28% *vs.* 29%), long-term follow-up showed that PLD significantly prolonged OS compared with topotecan (107.9 *vs.* 70.1 weeks; $p = 0.017$). Although the response rate was somewhat lower than that of platinum doublet regimens, it is difficult to compare results across studies owing to differences in patient populations.

There are some probable potential benefits of using non-platinum (especially PLD) single agents in patients with platinum-sensitive disease. First, it offers comparable response rates and long-term stable disease. Second, it avoids the cumulative side effects associated with the continued use of platinum and thus improves quality of life. Third, it may increase the subsequent response to platinum reintroduction by expanding the platinum-free interval and thus offers the best chance for long-term survival.

Ongoing trials (PLD with/without trabectedin, ET743-OVA-301)

This is a global, randomized controlled study comparing the combination of PLD (30 mg/m^2, 90-minute infusion) followed by trabectedin (1.1 mg/m^2, 3-hour infusion, every 3 weeks) with PLD (50 mg/m^2, 90-minute infusion, every 4 weeks) in patients with relapsed EOC. PLD and trabectedin have different mechanisms of action with different cellular targets and non-overlapping toxicity. From the preliminary PLD and trabectedin combination phase I study data in a variety of tumor types [63], the combination regimen provided an improved efficacy with an acceptable safety profile. Therefore, the rationale for the study is to determine whether the combination is superior over either agent alone. This ongoing trial proposed to enroll 650 patients over 2 years (till July 2007) from approximately 120 sites (six sites from Taiwan) all over the world. Additional 2–3 years may be required to observe the results.

Future Directions

A number of novel agents are being investigated to identify strategies more effective than conventional chemotherapy for the treatment of advanced EOC in both the frontline and recurrent settings. However, the measurement of the efficacy of these agents might need to be reassessed, since many of these agents might have cytostatic effects; and thus, the criteria applied to traditional cytotoxic compounds might be less applicable

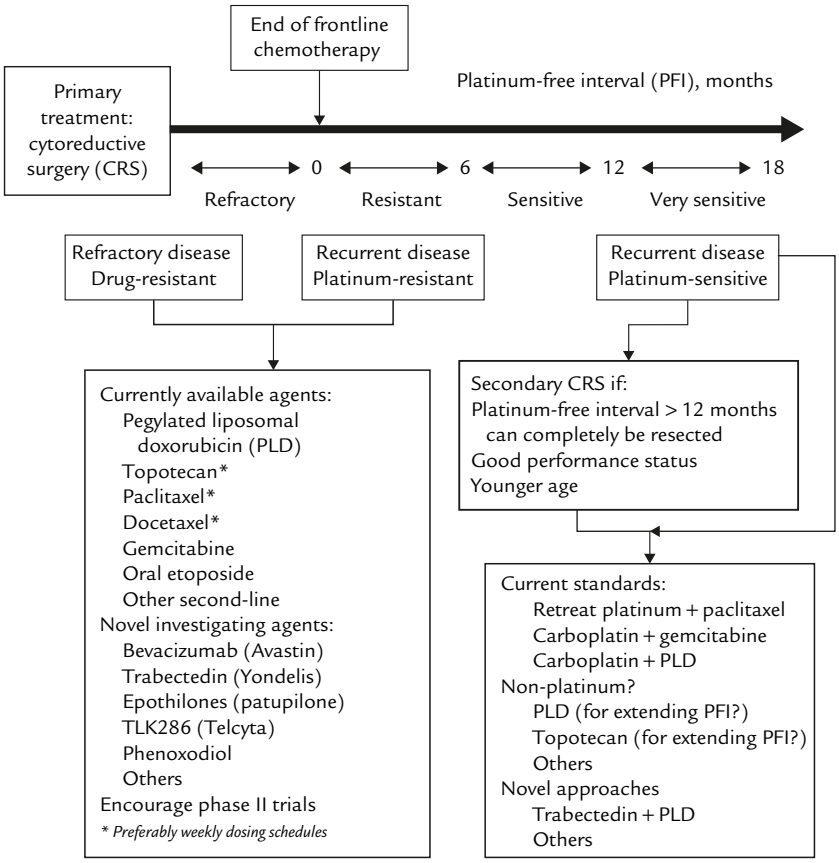

Figure 2. Management of patients with relapse/refractory epithelial ovarian cancer.

in determining the clinical benefit. Another great challenge is identifying the most relevant and clinically significant targets for ovarian cancer, since many of these cancers carry multiple molecular defects.

Conclusion

In defining the optimal therapeutic strategy for recurrent ovarian cancer, there is no widely accepted standard for platinum-refractory/resistant disease. In the absence of demonstrated superiority of combination regimen over single-agent regimen, the therapy in this clinical setting is sequential single-agent treatment and should be based on side-effect profile and other quality-of-life issues. The combination of paclitaxel with carboplatin, on the other hand, is considered as the standard chemotherapy for the treatment of relapsing patients with platinum-free interval over 6 months. Regimens substituting new drugs, such as gemcitabine or PLD, to paclitaxel in association with carboplatin may offer platinum-based combinations with better toxicity profile and quality of life. Selected platinum-sensitive patients with localized disease may also be suitable candidates for secondary cytoreductive surgery prior to the initiation of chemotherapy (Figure 2). In addition, the availability of several new drugs with activity in ovarian cancer has allowed a better control of recurrences with survival prolongation. However, even these strategies may not prove sufficiently effective, and continued study of molecular and genetic targeted therapies through vectors and monoclonal antibodies may ultimately be the only breakthrough. We hope that the next decade will yield significant progress in the treatment of this catastrophic disease.

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