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REVIEW

New developments in treatment of ovarian carcinoma: focus on trabectedin

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Abstract: Trabectedin is a new marine-derived compound that binds the DNA minor groove and interacts with proteins of the DNA repair machinery. Trabectedin has shown promising single-agent activity in pretreated patients with soft tissue sarcoma, and ovarian and breast cancer, and combination with various other chemotherapeutic drugs seems feasible. Toxicities are mainly hematologic and hepatic, with Grade 3–4 neutropenia and thrombocytopenia observed in approximately 50% and 20% of patients, respectively, and Grade 3–4 elevation of liver enzymes observed in 35%–50% of patients treated with trabectedin. The recently reported results of a large Phase III trial comparing pegylated liposomal doxorubicin (PLD) alone with a combination of PLD and trabectedin in patients with recurrent ovarian cancer showed improved progression-free survival with the combination of trabectedin and PLD, albeit at the price of increased toxicity. Current research focuses on the identification of predictive factors for patients treated with trabectedin, as well as the development of other combinations.

Keywords: chemotherapy, ovarian cancer, combination, drug development, DNA repair

Introduction

Epithelial ovarian cancer is the leading cause of death from gynecologic cancers in Western countries.[1,2] Most patients present with advanced disease (ie, Stage III and IV), and are managed with surgical resection followed by platinum-based chemotherapy.[3] During the past decade, advances in chemotherapy have resulted in improved survival and in more effective treatment of relapsed disease. However, five-year overall survival remains relatively low, at around 30%.[4]

The most important prognostic factors at primary diagnosis are International Federation of Gynecologists and Obstetricians (FIGO) stage and complete resection of disease (microscopic residual disease following primary surgery). The time point of relapse following the completion of chemotherapy defines the category of platinum sensitivity, ie, the longer the interval, the longer the duration of response likely to be achieved by platinum retreatment. Patients whose disease responds to first-line therapy but relapses ≥12 months after completion of initial platinum-based therapy are considered to have platinum-sensitive disease. Patients who relapse 6–12 months after primary therapy have intermediate or partial platinum-sensitive disease. Patients who relapse shortly (<six months) after the completion of primary therapy, are considered to have platinum-resistant disease. Patients who relapse during primary therapy are considered to have platinum-refractory disease.

Chemotherapy retreatment is an important aspect in the overall management of patients with platinum-sensitive relapse of recurrent ovarian cancer. Platinum is

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the backbone of chemotherapy for patients with advanced ovarian cancer, and carboplatin and paclitaxel have emerged as standard in the first-line setting. This combination is also regarded as a valid option for rechallenge in patients with platinum-sensitive recurrent ovarian cancer. A pooled analysis of three Phase III trials from the Arbeitsgemeinschaft Gynaëkologische Onkologie Studiengruppe Ovarialkarzinom and International Collaborative Ovarian Neoplasm collaborators demonstrated significant improvements in progression-free survival and overall survival in patients with platinum-sensitive recurrent ovarian cancer treated with platinum-paclitaxel versus conventional, mainly single-agent, platinum-based therapies.[5] However, rechallenge with carboplatin and paclitaxel has been limited by the risk of cumulative peripheral neuropathy. Other carboplatin-based combinations, such as gemcitabine and carboplatin, have been explored with the aim of improving both efficacy and tolerability. Carboplatin and gemcitabine significantly improved progression-free survival versus carboplatin alone in a Phase III trial (hazards ratio [HR] 0.72, $P = 0.0031$).[6] Overall survival, however, was not significantly improved (HR 0.96, $P = 0.735$), although the trial was not powered to detect a survival difference. Grade 3–4 hematologic toxicities were significantly more frequent in the combination arm. More recently, Pujade-Lauraine et al reported a Phase III trial comparing carboplatin and paclitaxel with carboplatin and pegylated liposomal doxorubicin (PLD) in patients with ovarian carcinoma relapsing more than six months after first- or second-line platinum- and taxane-based therapy.[7] In this trial, the largest in recurrent ovarian cancer, treatment with carboplatin and PLD was associated with improved progression-free survival (11.3 versus 9.4 months, $P = 0.005$) and a favorable safety profile.

Treatment options for patients with partial platinum-sensitive disease (six months $\leq$ platinum-free interval $<$ 12 months) include carboplatin-based doublets (either with paclitaxel or gemcitabine), which achieve progression-free survival durations of approximately eight months,[8] and PLD.[9] In this subset of patients, PLD was shown to be superior to topotecan in terms of both progression-free survival and overall survival,[10] although it has never been compared "head to head" with a platinum doublet. Overall survival in patients with partial platinum-sensitive disease recurrence is approximately 13–15 months. An emerging strategy in these patients is to "artificially" increase the platinum-free interval by using a nonplatinum-containing regimen upon relapse, with the aim of reversing platinum resistance.[11]

In patients with platinum-resistant or refractory recurrent ovarian cancer, treatment options are limited, and this patient subgroup has a poor prognosis. Agents that can be considered include PLD, topotecan, gemcitabine, paclitaxel, oral etoposide, and vinorelbine. Because the reported response rate for each of these drugs is in the 10%–20% range in patients with platinum-resistant disease, the choice is often driven by the side effect profile and the convenience of administration.[12] Topotecan and PLD have been more extensively studied in this setting, and seem to provide some benefit in progression-free survival, although rarely associated with an improvement in overall survival.

Trabectedin: a minor groove alkylator

Trabectedin (ET743, Yondelis®; PharmaMar, Madrid, Spain), a tetrahydroisoquinoline alkaloid, is a natural product derived from the marine tunicate *Ecteinascidia turbinate*. Trabectedin (ET743) binds to the minor groove of DNA and alkylates guanine at the N2 position, whereas most alkylating agents bind guanine at position N7 or O6 in the major groove. Binding of trabectedin has been shown to be DNA sequence-specific, with guanine-cytosine rich triplets more frequently bound.[13] Covalent binding of trabectedin induces DNA bending towards the major groove and a widening of the DNA minor groove.[14] Modification of the DNA conformation leads to inhibition of activated transcription, while constitutive transcription seems unaffected.[15]

ET743 has shown potent antitumor activity in preclinical studies both in vitro and in vivo in several solid tumors, including ovarian and breast cancer, melanoma, and sarcoma.[16,17] These preclinical data have been confirmed in several Phase II trials in soft tissue sarcoma, and breast and ovarian carcinoma. Trabectedin is approved in the European Union and several other countries for the treatment of relapsed soft tissue sarcoma which has progressed despite previous treatment with anthracyclines and ifosfamide, or in those who are unable to receive these agents. It is also approved in the European Union in combination with PLD for the treatment of platinum-sensitive recurrent ovarian cancer. In addition, trabectedin holds orphan drug status for the treatment of advanced recurrent soft tissue sarcoma in the US, Switzerland, and Korea, and for the treatment of advanced recurrent ovarian cancer in the US and Switzerland. Trabectedin is under development for prostate cancer, breast cancer, and pediatric soft tissue sarcoma.

Several reports have underlined the importance of nucleotide-excision repair in the cytotoxicity of ET743,

and more precisely the cell killing ability of this drug has been linked to transcription-coupled nucleotide-excision repair.[13,14,18] The DNA bending induced by the binding of trabectedin to the minor groove is detected by the transcription-coupled nucleotide-excision repair machinery, which in the repair process makes single-strand breaks on each side of the lesion.[13] These breaks are then made irreversible by the DNA-protein crosslinking capacities of trabectedin.[19] Recently Herrero et al[18] suggested a slightly different model based on their observations in the yeast model, *Schizosaccharomyces pompe*. In this model, cells deficient for Rad13 (the yeast equivalent to human XPG, an endonuclease of the nucleotide-excision repair system), were resistant to trabectedin, while those with an inactive Rad51 (a protein of the homologous recombination repair pathway, involved in the repair of double-strand breaks) were more sensitive to trabectedin than wild-type cells. Based on these observations, Herrero et al suggested the following sequence: trabectedin binds covalently to the DNA minor groove, the resulting adduct is recognized by the nucleotide-excision repair machinery, and then the recruited Rad13 (XPG) protein binds to DNA and interacts with the minor groove-bound drug by means of an arginine residue located in the COOH terminus. Other proteins of the nucleotide-excision repair machinery trying to repair the damage are then hijacked, forming larger, more toxic complexes. Lastly, during the S phase, the aforementioned complexes give rise to double-strand DNA breaks, explaining the sensitivity of cells deficient for homologous recombination repair pathway proteins (eg, Rad51).[18]

Single-agent trabectedin in advanced ovarian carcinoma

Three Phase II studies have investigated the activity of trabectedin in patients with recurrent advanced ovarian cancer (Tables 1 and 2). Based on preclinical data showing that trabectedin was active in xenograft models with low sensitivity to cisplatin or paclitaxel, Sessa et al[20] reported the results of a Phase II study of trabectedin in patients with ovarian cancer failing platinum- and taxane-based therapy. Fifty-nine patients were enrolled and stratified according to platinum sensitivity, ie, 30 patients with platinum-resistant disease (no change after at least four cycles of platinum or taxane, progressive disease after two cycles, or relapse within an interval of less than six months after discontinuation of chemotherapy) and 29 patients with platinum-sensitive disease (relapse after a progression-free interval of ≥six months after completion of platinum-based chemotherapy). Twenty-two (37%) patients had received at least two prior lines of treatment. Trabectedin was administered as a three-hour infusion every three weeks, initially given at the dose of 1650 μg/m² based on the recommended Phase II dose found in Phase I trials. The dose in this study was subsequently decreased to 1500 μg/m², and then to 1300 μg/m², because of toxicity (essentially liver toxicity). Systemic antiemetic prophylaxis with intravenous 5-hydroxytryptamine-3 antagonists and 10 mg of dexamethasone intravenously was mandatory, and patients took 4 mg of dexamethasone bid for prophylaxis against liver toxicity. Fifty-one patients were assessable according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria. The overall response rate in the 23 assessable patients with platinum-sensitive disease was 43.5%, (one complete response lasting 8.7 months and nine partial responses) and an additional nine patients had stable disease. Median time to progression for patients who achieved a partial response was 7.9 months. In the platinum-resistant stratum, the overall response rate was 7%, and two of 28 patients achieved a partial response lasting 4.0 and 4.6 months. Stable disease was achieved by eight additional patients (28.6%). At the higher dose level of 1650 μg/m² Grade 4 elevation of liver transaminases, asthenia, and nausea and vomiting were seen in 83%, 82%, and 50% of patients. At the 1300 μg/m² dose level, treatment was well tolerated with a transient increase in transaminases and Grade 3–4 neutropenia. Two patients (3%) in this study experienced febrile neutropenia (one at the 1650 μg/m² dose level and the other at the 1300 μg/m² dose level).[20]

Table 1 Summary of efficacy of trabectedin as a single agent in relapsed ovarian cancer

Study	PFI (months)	n	CR	PR	ORR	Median PFS (months)
Sessa et al[20]	<6 months	30	0	2 (7%)	7%	NR
	≥6 months	29	1 (3%)	9 (31%)	34%	NR
Krasner et al[21]	<6 months	81	0	5 (6%)	6%	2.0
	6–12 months	43	1 (2%)	9 (22%)	24%	4.0
	≥12 months	23	3 (13%)	5 (22%)	35%	5.1
Del Campo et al[22]	<6 months	7	0	1	14.3%	NR
	6–12 months	48	NR	NR	29.9%	5.6
	≥12 months	52	NR	NR	48.1%	10.8

Abbreviations: PFI, platinum-free interval; CR, complete response; PR, partial responses; ORR, overall response rate; NR, not reported.

The results of the second Phase II trial of trabectedin in patients with ovarian carcinoma were reported by Krasner et al.[21] This study enrolled 147 patients who had received no more than two prior platinum-containing regimens. Trabectedin was administered as a three-hour infusion weekly for three weeks of a four-week cycle at 580 μg/m², after premedication by 10 mg of intravenous dexamethasone.

Table 2 Summary of the most commonly encountered Grade 3–4 side effects in single-agent trials of trabectedin in patients with ovarian cancer

Study	Schedule	Infusion time (hours)	n	AST	ALT	Bilirubin	Neutropenia	Thrombocytopenia	Fatigue	Nausea vomiting
Sessa et al[20]	1650 μg/m²/3 wks	3	6	6 (100%)[a]	–	0	NA	NA	NA	NA
	1500 μg/m²/3 wks	3	12	10 (84%)[a]	–	0	NA	NA	NA	NA
	1300 μg/m²/3 wks	3	41	31 (75%)[a]	–	0	17 (41%)	3 (7%)	3 (7%)	2 (5%)
Krasner et al[21]	580 μg/m²/wk 3/4 wks	3	147	4 (3%)	18 (12%)	0	12 (8%)	4 (3%)	8 (5%)	8 (5%)
Del Campo et al[22]	1500 μg/m²/3 wks	24	54	19 (35%)	30 (56%)	0	29 (54%)	4 (8%)	8 (15%)	2 (4%)
	1300 μg/m²/3 wks	3	53	10 (19%)	31 (58%)	1 (2%)	20 (38%)	5 (10%)	4 (8%)	3 (6%)

Note: [a]Pooled data for AST/ALT elevation.
Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; wk, week.

One hundred and forty-one patients were evaluable by RECIST criteria, ie, 62 in the platinum-sensitive cohort (defined as relapse after a disease-free interval ≥ six months from the end of the last platinum-based chemotherapy) and 79 in the platinum-resistant cohort (defined as disease progression < six months from the end of the last platinum-based treatment). The overall response rate (by RECIST) was 29% in the platinum-sensitive cohort (four complete responses and 14 partial responses), and the median progression-free survival was 5.1 months. In the platinum-resistant cohort, the overall response rate was 6.3% (five partial responses) and the median progression-free survival was two months. Toxicity was much more manageable than in the European Phase II study, as a result of the weekly schedule and the lower initial dose intensity delivered. Nausea, vomiting, and fatigue were seen in 50%–60% of patients. The most common Grade 3–4 toxicities were elevated alanine transaminases (11%), neutropenia (6%), and nausea, vomiting, and fatigue (5% each).

Del Campo et al reported on a randomized Phase II study comparing two schedules of trabectedin, ie, 1500 μg/m² over 24 hours every three weeks (arm A) and 1300 μg/m² over three hours every three weeks (arm B), the primary endpoint being the response rate.[22] Patients received the recommended antiemetic prophylaxis with setron and dexamethasone. One hundred and eight patients were randomized between the two arms, and 107 received treatment. The intent to treat analysis showed comparable response rates between the two arms (38.9 in arm A, 35.8 in arm B, $P = 0.8422$). Likewise, the progression-free survival was similar in both arms (6.2 months in arm A, 6.8 months in arm B, $P = 0.3127$) suggesting that the two schedules have similar activity. The most common adverse events were nausea, vomiting, and fatigue, in most cases Grade 1 or 2. Hematologic toxicity was manageable, and mostly consisted of neutropenia and thrombocytopenia. Febrile neutropenia was seen in five patients (5%), and two patients died of possible drug-related adverse events.

McMeekin et al reported a pooled analysis of three Phase II studies, including 294 patients, in which three different schedules of administration were compared, one with 1300 μg/m² over three hours, one with 1500 μg/m² over 24 hours, both every three weeks, and one with 580 μg/m² weekly, for three weeks of a 28-day cycle.[23] However, no significant differences in efficacy were seen between the two every three-week schedules, as was seen in patients with sarcoma.[24] These two schedules were significantly superior to the weekly schedule, with a better response rate (33% versus 16%, $P \leq 0.0001$) and longer median time to progression (5.8 months versus 2.8 months, $P = 0.0001$).

Overall, these Phase II studies show that trabectedin has single-agent activity in patients with platinum-sensitive relapsed ovarian carcinoma, with a manageable toxicity profile. The activity of trabectedin in platinum-resistant disease seems more disappointing (Table 1), with reported response rates lower than those reported for other agents currently available, such as PLD, topotecan,[9] or gemcitabine.[25,26]

Trabectedin-based combinations

Several Phase I trials of trabectedin-based combinations have been reported, and showed that trabectedin could be safely combined with doxorubicin,[27,28] PLD,[29] gemcitabine,[30] taxanes,[31,32] and capecitabine.[33]

A recently published article has reported on a Phase I trial investigating the combination of trabectedin and cisplatin.[28] There is a strong preclinical rationale for this combination based on the mechanisms of action of both drugs which target different pathways of DNA repair (nucleotide excision repair for trabectedin and homologous recombination for cisplatin) and

on synergistic activity against human tumor xenografts. Sessa et al conducted a Phase I trial of trabectedin and cisplatin, both given on days 1 and 8 of a 21-day cycle.[28] Trabectedin was given as a three-hour infusion, starting at 300 μg/m² (with 100 μg/m² increments), and cisplatin at a fixed dose of 40 mg/m². Persistent neutropenia was the most common dose-limiting toxicity in this study, and several patients had not recovered from Grade 3 neutropenia by day 35. The recommended Phase II dose of trabectedin was 500 μg/m² on days 1 and 8 in pretreated patients and 600 μg/m² on days 1 and 8 in treatment-naive patients (combined with cisplatin 40 mg/m² on days 1 and 8). Although antitumor activity was seen with this combination, the results were lower than expected, especially in patients with ovarian carcinoma, and the response rate was comparable with that of single-agent trabectedin (with limitations due to the small sample size of n = 13). One of the hypotheses raised by the authors to explain these deceiving results is that the trabectedin dose intensity was insufficient due to prolonged dose delays.[28] Development of a three-week schedule was therefore suggested. However, it is noteworthy that these findings are in line with a previous Phase I trial of a combination of trabectedin and carboplatin where hematologic toxicity precluded a dose increase of trabectedin beyond 800 μg/m² every three weeks and carboplatin beyond an area under the concentration-time curve (AUC) of 4 mg/mL/min.[34]

Other interesting candidates for combination with trabectedin in patients with ovarian cancer include gemcitabine, PLD, and the taxanes. Data on these combinations are summarized in Table 3.

Messersmith et al conducted a Phase I trial exploring the combination of trabectedin and gemcitabine.[30] Both drugs were administered on days 1, 8, and 15 of a 28-day cycle. Two dose levels were planned for gemcitabine (800 and 1000 mg/m²) and five were planned for trabectedin (300, 400, 475, 535, and 580 μg/m²). Fifteen patients were enrolled, of whom five had sarcomas, three had non-small-cell lung cancer, two had colorectal cancer, and two had renal cell carcinoma. All patients but one were pretreated with chemotherapy and 12 patients had received at least two prior regimens. This study was terminated early because of an unacceptable frequency of dose adjustments due to hepatic toxicity. Patients received a median of two (range 1–10) treatment cycles. The dose-escalation scheme was stopped at level 3 (trabectedin 400 μg/m² and gemcitabine 1000 mg/m²) where four of six patients required dose hold/cycle delay. Overall cycle delays and dose holds were required in 11 (of 15) patients, in most cases during the two first cycles and most often related to liver toxicity. Dose reductions were required for trabectedin in four patients and gemcitabine in six patients. Dose-limiting toxicity was defined as any of the following during the first cycle: Grade 4 neutropenia (absolute neutrophil count < 500/mL) for > five days; febrile neutropenia (absolute neutrophil count < 500/mL with fever [body temperature 38.5°C] or sepsis); thrombocytopenia (platelets < 25,000/mL); any Grade 3 nonhematologic toxicity (except nausea/vomiting and Grade 3 transaminitis lasting < one week); or delay of continuation of therapy > three weeks. Dose reductions were not considered as dose-limiting toxicities. No dose-limiting toxicities were seen in any of the cohorts. The most frequently reported Grade 3 or 4 adverse event was alanine transaminase increase (33%). Although the study was terminated without reaching the maximum tolerated dose, toxicity appeared potentially manageable without evidence of a significant pharmacokinetic interaction with this combination. No objective response was noted, but two patients in this study had stable disease for more than six months. The recommended dose for future trials investigating this combination was trabectedin 400 μg/m² combined with gemcitabine 1000 mg/m² weekly for three weeks every four weeks.

von Mehren et al conducted a Phase I study to assess the maximum tolerated dose, safety, and potential pharmacokinetic interactions of trabectedin in combination with PLD.[29] Thirty-six patients with normal liver function, prior doxorubicin exposure < 250 mg/m², and normal cardiac function were enrolled. A broad range of advanced malignancies was represented, the most common being sarcoma (n = 16), ovarian cancer (n = 4), and pancreatic cancer (n = 2). Twenty-seven patients (75%) were pretreated with chemotherapy, with a median of three prior regimens. PLD was administered at the dose of 30 mg/m² with a one-hour infusion, and followed immediately by one of six trabectedin doses (400, 600, 750, 900, 1100, and 1300 μg/m²) infused over three hours and repeated every 21 days. All patients received dexamethasone 4 mg/day orally on the day before chemotherapy and on days 2 and 3 of each cycle, as well as 20 mg intravenously on day 1. Dose-limiting toxicity was defined as the following during cycle 1: an absolute neutrophil count < 500/mL for >five days or with fever or sepsis; platelet count < 25,000/mL; any Grade 3 or 4 nonhematologic toxicity (except for nausea/vomiting despite appropriate antiemetic treatment or Grade 3 transaminase elevations lasting < one week); or a delay of therapy for >three weeks. The median number of cycles was four. The maximum tolerated dose was PLD 30 mg/m² + trabectedin 1100 μg/m². Dose-limiting toxicities occurred in two patients in the 1300 μg/m² cohort during

Table 3 Summary of data on trabectedin-based combination of potential interest in ovarian cancer

Combination	Reference	Schedule	Recommended Phase II dose	Dose-limiting toxicity	Efficacy in ovarian cancer patients	Comments
Trabectedin Cisplatin	27	Days 1 and 8 every 21 days Days 1 and 8 every 21 days	500–600 μg/m² 40 mg/m²	Prolonged neutropenia	Four of 13 patients (31%) with OC had a PR	Deceiving efficacy-wise and toxic
Trabectedin Gemcitabine	29	Days 1, 8 and 15 every 28 days Days 1, 8 and 15 every 28 days	400 μg/m² 1000 mg/m²	None	NR	
Trabectedin PLD	28	Day 1 every 21 days Day 1 every 21 days	1100 μg/m² 30 mg/m²	Grade 3–4 transaminitis lasting > 7 days	One patient with PPC had a PR and 2 of 4 patients with OC has SD	A subsequent phase III trial in patients with ROC showed improved RR and PFS compared with PLD alone
Trabectedin Docetaxel	30	Day 1 every 21 days Day 1 every 21 days	1100 μg/m² 60 mg/m²	Grade 4 neutropenia and/or febrile neutropenia before primary prophylaxis with filgrastim. Grade 3 fatigue.	NR	A subsequent phase II trial in patients with ROC showed a RR, PFS and OS of 30%, 4.4 months and 12.5 months respectively
Trabectedin Paclitaxel	31	Day 2 every 14 days Day 1 every 14 days	650 μg/m² 120 mg/m²	Grade 4 neutropenia lasting 5 days or more, dose delays beyond 8 days	One patient with OC has PD (no response)	

Abbreviations: PLD, pegylated liposomal doxorubicin; OC, ovarian cancer; ROC, relapsed ovarian cancer; PR, partial response; NR, not reported; RR, response rate; PFS, progression-free survival; OS, overall survival; PD, progressive disease; SD, stable disease.

cycle 1, consisting of Grade 3 or 4 transaminase elevations lasting > seven days. The most frequent Grade 3 or 4 drug-related events were alanine transaminase elevations (31%) and neutropenia (31%). Transaminase elevations resolved without specific intervention and were successfully managed with dose reductions. Post-treatment liver biopsies were carried out in eight patients who had elevations in liver function tests, and nonalcoholic steatohepatitis was present in seven of eight biopsies. Six patients had an asymptomatic reduction of left ventricular ejection fraction of ≥20% versus baseline. Only one of these six patients had received a prior anthracycline-based regimen, although all six had a cumulative exposure to anthracyclines of ≥300 mg/m² (range 365–690 mg/m²) when noted to have a change in the left ventricular ejection fraction. Finally, one complete response and five partial responses (overall response rate 16.7%) were seen and 14 patients had stable disease. The majority of responses occurred in the 1100 μg/m² and the 1300 μg/m² cohorts. Overall, these data show that trabectedin combined with PLD is feasible with encouraging activity. The regimen comprising PLD 30 mg/m² plus trabectedin 1100 μg/m² was selected for a Phase III trial comparing PLD alone with PLD plus trabectedin in patients with advanced ovarian cancer failing one prior platinum-based regimen.

von Mehren et al reported the results of a Phase I trial of docetaxel 60 mg/m² combined with trabectedin as a three-hour infusion on day one of a three-week cycle.[31] Six dose levels (400 μg/m² through to 1300 μg/m²) and two independent cohorts, ie, "restricted" (≤one prior regimen) and "unrestricted" (no limits as to the number of previous regimens) were planned. Thirty-four patients were enrolled, 10 of whom had sarcoma. Five patients developed dose-limiting toxicity at the 600 μg/m² dose level, ie, Grade IV neutropenia and/or febrile neutropenia requiring institution of prophylactic filgrastim. After institution of filgrastim, only one dose-limiting toxicity (fatigue) was observed at the 1300 μg/m² dose level. The most frequent Grade 1–2 adverse events were fatigue (68%), nausea (58%), and neutropenia (53%). Preliminary data suggest activity for this combination in patients with advanced cancer, with one patient achieving

a complete response and 17 maintaining prolonged stable disease. A subsequent Phase II trial in patients with recurrent ovarian cancer used doses of 60 mg/m² for docetaxel and 1100 µg/m² of trabectedin given every three weeks. In the preliminary report of this trial, the response rate was 30%, and the median progression-free survival and overall survival were 4.4 months and 12.5 months, respectively.[35]

In their Phase I study, Chu et al administered escalating doses of paclitaxel (80–120 mg/m²) over one hour on day 1 and trabectedin (525–775 µg/m²) as a three-hour infusion on day 2 every two weeks.[32] Twenty-nine patients were enrolled, including 23 patients with soft tissue sarcoma, and 27 patients were evaluable. Two doses were planned for paclitaxel (80 mg/m² or 120 mg/m²) and four doses for trabectedin (525, 580, 650, or 775 µg/m²), and five schedules were tested. There were four dose-limiting toxicities due to neutropenia delaying therapy for more than one week, two of which occurred on paclitaxel 120 mg/m² + trabectedin 775 µg/m². Therefore, the recommended dose was paclitaxel 120 mg/m² + trabectedin 650 µg/m². The most common toxicities were neutropenia (24%), nausea (51%), vomiting (24%), transaminitis (23%), myalgia (24%), and alopecia (20%). Evidence of antitumor activity and clinical benefit was seen, with one patient who had a primitive neuroectodermal tumor showing an ongoing complete response at 19+ months, one patient with breast cancer (prior paclitaxel failure) having an unconfirmed partial response, and eight patients having stable disease for more than three months.

Trabectedin–PLD combination in relapsed ovarian carcinoma

Based on the activity of both PLD and trabectedin in patients with relapsed ovarian carcinoma, together with a favorable safety profile described in Phase I investigations, a Phase III trial comparing a combination of PLD and trabectedin with PLD alone in patients with recurrent ovarian cancer was initiated. Six hundred and seventy-two patients progressing after initial response to first-line platinum-based therapy and with measurable disease were randomized to a combination of PLD 30 mg/m² over 60 minutes and trabectedin 1100 µg/m² over three hours every 21 days (PLD + T, with 10 mg intravenous dexamethasone 30 minutes prior to trabectedin infusion) or standard PLD 50 mg/m² once every four weeks. Patients experiencing disease progression during platinum-based front-line therapy were excluded.[36] Progression-free survival was the primary study endpoint and was assessed by independent radiologic review. Baseline characteristics were comparable between arms, ie, median age was 57 years, 421 patients (63%) had platinum-sensitive disease (platinum-free interval for more than six months). The median number of cycles was five for PLD and six for PLD + T. Median progression-free survival for the combination arm was 7.3 months (95% CI 5.9–7.9) and 5.8 months (95% CI 5.5–7.1) for single-agent PLD (HR = 0.79, $P = 0.019$). For patients with platinum-sensitive disease (platinum-free interval more than six months), the median progression-free survival was 9.2 months (95% CI 7.4–11.1) for the combination arm versus 7.5 months (95% CI 7.0–9.2) for PLD alone (HR 0.73, $P = 0.017$). Objective response rate for all patients was 28% versus 19% ($P = 0.008$) and 35% versus 23% ($P = 0.0042$) for patients with platinum-sensitive disease. In the platinum-resistant subgroup, there was no benefit in progression-free survival (4.0 versus 3.7 months for PLD + T and PLD, respectively) nor in response rate (overall response rate 16% versus 15% for PLD + T and PLD, respectively). There was no overall survival difference between the two arms, ie, 20.5 months for PLD + T versus 19.4 months for PLD alone (HR 0.85, $P = 0.15$). However, follow-up was insufficient at the time of reporting. Sixteen percent of patients in the combination arm and 10% in the single-agent PLD arm discontinued treatment because of adverse events. Grade 3 and Grade 4 adverse events included neutropenia (63% versus 22%), elevated alanine transaminase (31% versus 1%), and hand-foot syndrome (4% versus 20%) for PLD + T versus PLD alone, respectively. On the basis of these results, the authors concluded the superior efficacy the PLD + T combination, which also demonstrates competitive efficacy compared with previously described platinum-based combinations in patients with platinum-sensitive relapsed ovarian cancer.

Despite these conclusions, the FDA denied approval for the combination of trabectedin and PLD in patients with relapsed ovarian carcinoma. One of the reasons was that the FDA panel felt that the six-week benefit in progression-free survival shown in this trial did not justify approval of the drug. Progression-free survival has not been proven to be a valid surrogate for overall survival in patients with relapsed ovarian cancer, and the increment itself is relatively low given the added toxicity. Furthermore, although PLD is an option in patients with relapsed platinum-sensitive disease, platinum-based therapy may be regarded as the preferred treatment in this patient subgroup. Therefore, given the fact that this study included a majority of patients with platinum-sensitive disease, the validity of the comparator may be questioned. Another point of discussion is the lack of benefit in patients with platinum-resistant disease, although this is in line with previous data showing that trabectedin has little efficacy in this patient subgroup.[20–22] Finally, there was an increase in

the rate of nonfatal congestive heart failure-related events in the trabectedin group (six events for PLD + T versus one for PLD alone).[36]

Interestingly, a subgroup analysis of this study, reported at the 2010 ASCO meeting, suggested that patients with partial platinum-sensitive disease may benefit the most from this combination.[37] Indeed, 214 patients in this trial had partial platinum-sensitive disease. In this subgroup, the median progression-free survival was 7.4 months for patients treated in the combination arm (T + PLD) versus 5.5 months for patients treated with PLD alone. Furthermore, this benefit translated into an overall survival advantage of 3.5 months (20.7 versus 17.2, $P = 0.009$). Two comments can be made on these results. First, because there was no crossover in this study, one cannot rule out that giving sequential single-agent PLD followed by trabectedin at progression may be as or even more effective than the combination. Second, we still need more follow-up to assess overall survival in the whole cohort.

In another subgroup analysis of this trial, investigators sought to identify predictive factors for patients receiving trabectedin.[38] This study focused on proteins of the nucleotide-excision repair and homologous recombination repair pathways because these pathways are important for trabectedin activity in vitro. The markers studies included ERCC1, XPG (both part of the nucleotide-excision repair machinery), and BRCA1 (homologous recombination repair pathway), and their expression was studied using real-time polymerase chain reaction on prechemotherapy tumor blocks. Patients with low BRCA1 mRNA levels had significantly longer overall survival ($P = 0.0297$) and progression-free survival ($P = 0.0427$) than those with high BRCA1 levels, thereby confirming the prognostic value of BRCA1 expression in patients with ovarian carcinoma.[39] A trend ($P = 0.0765$) for longer overall survival (but not progression-free survival) was found for patients with high ERCC1 expression levels. No significant differences in progression-free survival or overall survival emerged for low or high XPD expression levels. No significant differences in progression-free survival or overall survival were observed with the combined expression of BRCA1 and ERCC1. Caveats of these analyses include low numbers of patients with samples available and/or of adequate quality (139 of 672 patients, 20%), prior platinum-based therapy in all patients (and 80% prior taxanes) which might have modified the tumor RNA expression levels.

Other new agents in ovarian cancer

Several agents are currently in development in ovarian cancer, and can be grouped into three classes, ie, antiangiogenic agents, cell surface-targeted agents, and poly-adenosine triphosphate (ADP) ribose polymerase inhibitor.

Bevacizumab has shown promising results in several Phase II trials, and the Gynecologic Oncology Group GOG218 Phase III trial was recently reported at the 2010 ASCO meeting, showing improved progression-free survival for patients receiving first-line carboplatin-paclitaxel and bevacizumab, with bevacizumab maintenance therapy. Interestingly, the progression-free survival in the chemotherapy and bevacizumab without maintenance bevacizumab arm was not significantly different from that of the standard arm (carboplatin-paclitaxel alone). This trial therefore raises the question as to whether bevacizumab should be given as a maintenance therapy only, or whether it really needs to be combined in the initial chemotherapy regimen. Furthermore, the improvement in progression-free survival is limited, especially given that maintenance bevacizumab was given every three weeks for 16 cycles (approximately 11 months), and there is currently no overall survival advantage for patients receiving bevacizumab (insufficient follow-up). Therefore, it seems reasonable to wait for the overall survival data to mature, as well as data from other randomized trials (ICON7 trial), before we incorporate bevacizumab as part of standard practice.

Several antiangiogenic tyrosine kinase inhibitors (TKIs) are currently under active investigation in the treatment of advanced ovarian cancer. Cediranib, an oral TKI of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, and c-kit, showed interesting single-agent activity in a recently published Phase II trial in patients with relapsed ovarian carcinoma.[40] BIBF1120, a TKI targeting the VEGF, the platelet-derived growth factor, and the fibroblast growth factor receptor, has shown promising activity as maintenance therapy in a randomized Phase II trial.[41] Pazopanib, another TKI targeting the VEGF and platelet-derived growth factor receptor, has shown some activity in patients with biochemical relapse of ovarian cancer.[42] Both of these agents are currently being evaluated in Phase III trials, either in combination (BIBF1120) or as maintenance therapy (pazopanib).[4]

Cell surface targets in ovarian carcinoma include CA-125 and epithelial cell adhesion molecule. However, the current role of the relevant agents (oregomovab, abagomovab, and catumaxomab) in the management of patients with advanced ovarian cancer remains unclear, owing to the lack of a specific trial.

The most recent class of drug developed for patients with advanced ovarian cancer includes the poly-(ADP-ribose)-polymerase (PARP) inhibitors. This class of compound

targets PARPs, which are DNA repair enzymes. Preclinical experiments have shown synthetic lethality in cells deficient in BRCA 1 or BCRA 2.[43,44] A single-agent Phase I trial showed interesting activity in tumors from BRCA 1 or BRCA 2 mutation carriers, with a favorable toxicity profile.[45] Gelmon et al reported a Phase II trial in triple-negative breast and high-grade serous ovarian carcinoma demonstrating significant activity of single-agent olaparib in non-BRCA-mutated patients with advanced high-grade ovarian carcinoma.[46] However, an analysis of the expansion cohort of the Phase I study of olaparib in BRCA mutation carriers showed a correlation between response and duration of the platinum-free interval, suggesting that PARPs may not be as active in patients with platinum-resistant disease.[47] PARP inhibitors can also be combined with standard chemotherapy, most notably with DNA-damaging agents, with which they are most likely to be synergistic. Only Phase I trials have been reported to date for patients with ovarian carcinoma.

Conclusion

Trabectedin, a new marine-derived compound, has shown interesting activity in patients with platinum-sensitive relapsed ovarian carcinoma. However, several agents are currently approved for this indication, including paclitaxel, gemcitabine, and PLD. The standard of care in this setting remains the combination of carboplatin and paclitaxel, and a recent Phase III study showed improved progression-free survival and overall survival with weekly paclitaxel coupled with carboplatin for patients with platinum-sensitive recurrent ovarian cancer.[48]

When combined with PLD, trabectedin improved progression-free survival over PLD alone, although no overall survival advantage has yet emerged.[36] Furthermore, the progression-free survival benefit is numerically small (six weeks) and comes at the price of a significant increase in toxicity, although somewhat different from those seen with platinum or platinum-taxane regimens which are standard for this indication. Another drawback of this study is that single-agent PLD cannot be considered as standard in patients with platinum-sensitive relapsed ovarian cancer. Based on these observations, the use of trabectedin in the management of patients with platinum-sensitive disease cannot be clearly defined, and more studies are needed. However, recent data indicate that patients with partial platinum-sensitive disease benefit from the combination of trabectedin and PLD compared with PLD alone, with superior progression-free survival and overall survival for the combination.[37]

Disclosure

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