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REVIEW

Palliative systemic therapy for women with recurrent epithelial ovarian cancer: current options

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Objectives: To review the available systemic treatments for women with recurrent ovarian cancer.

Methods: A literature review was conducted for recurrent ovarian cancer articles in English, including randomized trials, Phase II trials, or reviews.

Results: We discuss the efficacy and toxicity outcomes associated with systemic therapy for platinum-sensitive and platinum-resistant ovarian cancer. Clearly, platinum-based combination systemic therapy shows a prolonged progression-free interval compared with single-agent chemotherapy with a low toxicity profile. No clear superior management strategy exists for platinum-resistant/refractory disease. Novel targeted antiangiogenic agents (eg, bevacizumab), angiopoeitin inhibitors (eg, AMG 386), and poly ADP ribose polymerase inhibitors (eg, olaparib) are reviewed.

Conclusion: Although combination platinum-based chemotherapy has shown benefits for women with platinum-sensitive recurrent ovarian cancer, the optimal treatment strategy for those with platinum-resistant or platinum-refractory disease is not clear. Molecular and genetic targeted therapies may provide opportunities for those women with tumor profiles that show sensitivity for specific agents.

Keywords: ovarian cancer, systemic therapy, biologic agents

Introduction

Ovarian cancer (OC) affects 2600 women annually in Canada for an incidence of eleven per 100,000.[1] This makes OC the eighth most common cancer in Canadian women. Annually, 1750 women will die of OC, which equates to a mortality rate of seven out of 100,000; thus, the case fatality rate is relatively high at 0.64. Approximately one in 100 women will die of OC, making it the fifth most common cause of cancer death in Canadian women. Treating women with OC with surgery and adjuvant chemotherapy has extended the duration of survival; however, the overall survival (OS) for women is still only 45% at 5 years.[2] What makes this disease difficult to manage is that 75%–85% of women present with disease spread throughout the abdominal cavity (advanced disease). Although 80% of patients respond to first-line treatment with platinum-based chemotherapy, most experience disease recurrence and, in these women in particular, OS is low.[3] Some physicians suggest that any patient who presents with epithelial OC (EOC) is palliative; however, patients who are appropriately staged and are found to have stage 1 disease can have a 5-year relative survival of 85%; therefore, for the purposes of this paper, we will consider palliative systemic therapy as medical management offered to women with recurrent disease.

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At the end of first-line chemotherapy, women may find themselves in one of three situations. Most commonly during first-line chemotherapy, the disease regresses. Firstly, it may completely resolve both by clinical, CA125, and computed tomography scan assessment. Secondly, in some instances, the disease burden is smaller but still present. Thirdly, platinum refractory usually describes a situation in which the disease has actually progressed during or shortly after chemotherapy. This group of women is unlikely to respond to any future cytotoxic therapy.

When disease recurs, the situation is considered palliative as the patients will eventually die of their disease. Markman et al[4] initially showed, in a retrospective analysis of 72 women treated with a platinum-based regimen, that the treatment-free interval predicted response to subsequent chemotherapy. If the treatment-free interval was 5–12 months, 27% responded to subsequent platinum-based chemotherapy; if 13–24 months, then 33% responded; if more than 24 months, then 59% responded.[4] Eisenhauer et al[5] analyzed the results of clinical trials involving 704 women with recurrent OC. They showed that predictors of response from second-line chemotherapy include whether or not the bulk of the disease is 5 cm, the number of disease sites, and serous histology. The treatment-free interval was not an independent factor, but rather correlated with tumor size.[5] However, time to recurrence is a readily available parameter that predicts the likelihood of responding to further treatment. Physicians continue to use this variable as a prognostic factor for planning subsequent treatment. Any discussion about the benefits of treatment should take into consideration efficacy (time to symptomatic disease, reduction of symptoms, prolong OS), the side effect profile and quality of life (QOL), patient convenience, cost, and patient preference.

Most physicians define subsequent therapy based on the patient's disease-free interval. Platinum sensitive describes two groups of women: first, are patients who recur more than 12 months after therapy, and second are those who are partially platinum-sensitive whose response lasted 6–12 months since the last platinum-based chemotherapy. This group of women is most likely to respond to chemotherapy again even though the duration of response will likely be less than with first-line treatment.[6] Platinum is the most active single agent in the list of available agents for treating OC. Platinum-based combinations provide a superior response rate compared to single-agent platinum for these women; however, benefits to OS are not clear. "Platinum-resistant" describes women with disease recurrence that occurs less than 6 months since the last platinum-based chemotherapy. "Platinum-refractory" describes women that never show any meaningful response to platinum therapy. Agents for platinum-resistant or -refractory disease generally provide a response rate of 10%–20% or less.[7,8]

In this paper, we will review the evidence for treating women with recurrent OC in terms of outcome (OS, disease-free survival, recurrence rate, toxicity profile, and QOL). We will also review the current literature in the context of both chemotherapy and biologic agents. Where randomized trials exist, we will focus on the results of such trials. Where only Phase II data exist, this evidence will be presented.

Literature review

To complete this review, a literature search was conducted using MEDLINE (1996–2011), and a review of guidelines such as the Canadian Medical Association Infobase and National Guidelines Clearing House was performed. In addition, relevant abstracts that were published in the proceedings of the American Society of Clinical Oncology and the European Society of Medical Oncology were reviewed.

Chemotherapy

Platinum-sensitive disease (>6 months)

Single-agent versus combination chemotherapy

There are a number of single-agent chemotherapy drugs that have been evaluated in women with platinum-sensitive OC. Two such drugs, carboplatin and cisplatin, have equivalent response rates in the order of 50%. In contrast, nonplatinum single agents in platinum-sensitive disease (eg, paclitaxel, topotecan, and pegylated liposomal doxorubicin [PLD]) have a 20%–30% response rate.[9,10] In general, randomized trials show that response rates, median progression-free survival (PFS), and OS rates are superior for platinum-based combination chemotherapy compared to single-agent platinum chemotherapy (Table 1).[11–19] Toxicities associated with repeat treatments with platinum and taxane include grade 2–4 neurologic toxicity in 20% of patients.[11,12] In patients treated with platinum and gemcitabine, grade 3–4 hematologic toxicity occurred in 78.3% of patients,[13] and the platinum hypersensitivity reaction rate was 18.8%.[14]

Thus, current guideline recommendations are that women in whom OC recurs after more than 12 months should be retreated with platinum-based chemotherapy.[20] Women with recurrence from 6–12 months after treatment would benefit from platinum combination, but the type of treatment depends on persistent toxicities from prior adjuvant treatments.[20]

Table 1 Single versus combination chemotherapy for recurrent ovarian cancer

Study	N	Regimen	RR	Median PFS	OS
Bolis et al[14]	95	Carboplatin	56%	12%, 3 years	29%, 3 years
	95	Carboplatin + epidoxorubicin	62%	25%, 3 years	42%, 3 years
			NS	NS	NS
Cantú et al[15]	50	Paclitaxel	45%	9 months	26 months
	47	CAP	55%	16 months	35 months
			NS	$P = 0.038$	$P = 0.043$
Parmar et al[11]	392	Carboplatin	54%	9 months	24 months
ICON4/AGO-OVAR2.2	410	Carboplatin + paclitaxel	66%	12 months	29 months
				$P = 0.0004$	$P = 0.02$
					HR 0.82
Gonzalez-Martin et al[12]	40	Carboplatin	50%	8 months	73 weeks
GEICO	41	Carboplatin + paclitaxel	75%	11 months	Pending
			$P = 0.05$	$P = 0.02$	
Pfisterer et al[13]	178	Carboplatin	31%	5.8 months	17.3 months
AGO-OVAR2.5	178	Carboplatin + gemcitibine	47%	8.6 months	18 months
GCIG			$P = 0.0016$	$P = 0.0031$	HR 0.96
				HR 0.76	
Alberts et al[16]	30	Carboplatin	32%	8 months	18 months
	31	Carboplatin + liposomal doxorubicin	67%	12 months	26 months
			$P = 0.02$		$P = 0.02$
Markman et al[17]	30	Carboplatin	28%	8 months	18 months
SWOG	31	Carboplatin + PLD	59%	12 months	31 months
					$P = 0.2$
Monk et al[18]		PLD	18.8%	5.8 months	NS
		PLD + trabectedin	27.6%	7.3 months	

Abbreviations: HR, hazard ratio; N, number; NS, not significant; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; RR, relative risk.

Combination chemotherapy

Table 2 outlines the various combination chemotherapy agent trials in this population. The median PFS shows a benefit for carboplatin-PLD and carboplatin treatment with weekly paclitaxel regimens.[19,21] Five-year survival data is currently not available (Table 2).[19,21,22] The toxicity profiles included severe nonhematologic toxicity (36.8% for carboplatin paclitaxel versus 28.4% for carboplatin PLD; $P < 0.01$) leading to early discontinuation (15% versus 6%, respectively; $P < 0.001$).[19] For the carboplatin and paclitaxel arm, there were more frequent grade two alopecia (83.6% versus 7%), hypersensitivity reactions (18.8% versus 5.6%), and sensory neuropathy (26.9% versus 4.9%).[19] For the carboplatin-PLD arm, there was more hand–foot syndrome (grade 2–3, 12% versus 2.2%), nausea (35.2% versus 24.2%), and mucositis (grade 2–3, 13.9% versus 7%).[19] Dose-dense platinum/taxane had a similar toxicity profile compared to every 3-week treatment of paclitaxel with the exception of a higher rate of grade 3–4 anemia.[21]

Platinum-resistant recurrent disease

Single-agent nonplatinum chemotherapy

Single agents that have been evaluated in a Phase II or III setting include hexamethamelamine, docetaxol, epirubicin,

Table 2 Comparison of combination chemotherapy agents in platinum-sensitive recurrent disease

Study	N	Regimen	Median PFS	Median OS
Pujade-Lauraine et al[19]	467	Carboplatin + liposomal doxorubicin	11.3 months	Not reached
			HR 0.821; 95% CI 0.72–0.94	
	509	Carboplatin + paclitaxel	9.4 months	
HECTOR[22]		Carboplatin + topotecan	Study completion estimated for September 2013	
NCT00437307		Carboplatin and other drug		
Katsumata et al[21]		Carboplatin + taxol weekly	28 months	72.1% at 3 years
JGOG 3016		Carboplatin + taxol q3wk	17.2 months	65.1%
			$P = 0.0015$	$P = 0.03$

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number; OS, overall survival; PFS, progression-free survival.

oral etoposide, gemcitabine, ifosfamide, tamoxifen, weekly paclitaxel, topotecan, vinorelbine, PLD, and irinotecan. With these compounds, disease response rates are 20% or lower (Table 3),[22–26] and no agent demonstrated superior efficacy. The duration of response was in the order of 4 months, with a median OS of 9–12 months.

Combination compared to single agent chemotherapy

Six randomized trials of combination versus single-agent chemotherapy in resistant OC (or where the majority of patients had resistant disease) failed to show superiority of combination chemotherapy over single-agent treatment (Table 4);[18,28–32] however, toxicity increased when a combination of agents was used. Hence, sequential use of single agents should be considered the treatment of choice over combination chemotherapy for women with platinum-resistant disease. A patient's performance status, efficacy, toxicity, ease/mode of administration, and QOL issues should be the most important determinants when selecting what agent to use. Preferably, patients should participate in trials of novel agents where symptom control and QOL are included as end points.

Other chemotherapy agents

Trabectedin (ET-743)

Trabectedin is a marine-derived chemotherapeutic agent. It was originally discovered in the colonial tunicate *Ecteinascidia turbinate*, and it is not synthetically produced. It binds to the minor groove of DNA and interferes with cell division and genetic transcription and DNA repair. In a Phase II study in women with platinum-refractory/resistant OC, the objective response rate was 7%, compared to 43% in the platinum-sensitive group.[33] Toxicities included grade 3–4 neutropenia in 41% and thrombocytopenia in 8% of patients.

Epothilones (patupilone)

Epothilones are a class of nontaxane microtubule-stabilizing agents obtained from the fermentation of the cellulose-degrading myxobacteria. Patupilone (an Epothilone B) showed a 16% overall response rate in OC patients with platinum-refractory/resistant recurrent disease.[34] A randomized parallel multicenter Phase III trial of patupilone compared to PLD was performed in women with platinum-refractory/resistant EOC: patupilone offered no OS benefit when compared to PLD.[35] Toxicities, such as grade 3–4 diarrhea, occurred in 17% and fatigue in 14% of women exposed to patupilone.

Targeted agents

Angiogenesis

Angiogenesis refers to the ability of a tumor to stimulate new blood vessel formation. For a tumor to grow beyond 1–2 mm in size, it needs to induce the formation of new blood vessels to supply its nutritional and other needs. Angiogenesis is needed for cancer cell growth, invasion, and metastasis. By targeting the angiogenic process, the supply of nutrients and oxygen to a tumor can be cut off, thus preventing tumor growth and spread to other parts of the body. All currently approved antiangiogenic drugs block either vascular endothelial growth factor (VEGF) or VEGF tyrosine kinase receptors (VEGFR).[36] These agents have been used either as single agents or in combination with conventional chemotherapeutic regimens.

Table 3 Nonplatinum chemotherapy in platinum-resistant recurrent disease

Study	N	Regimen	% platinum-resistant (<6 months)	Overall RR	Platinum-resistant RR	Median PFS	Median OS
ten Bokkel	114	Paclitaxel	52%	13%	7%	14 weeks	43 weeks
Huinink et al[24]	112	Topotecan	54%	21%	13%	23 weeks	61 weeks
Gordon et al[23]	239	Liposomal doxorubicin	54%	20%	12%	18 weeks	60 weeks
	235	Topotecan	53%	17%	7%	17 weeks	57 weeks $P = 0.038$
O'Byrne et al[25]	107	Liposomal doxorubicin	60%	19%		22 weeks	46 weeks
	107	Paclitaxel	63%	23%		22 weeks	56 weeks
Gore et al[26]	266	Topotecan (PO)		13%	8%	13 weeks	51 weeks
		Topotecan (IV)		20%	8%	17 weeks	58 weeks
Mutch et al[27]	195	Liposomal doxorubicin			8.3%	3.1 months	13.5 months
		Gemcitabine			6.1%	3.6 months	12.7 months

Abbreviations: IV, intravenously; N, number; OS, overall survival; PFS, progression-free survival; PO, oral administration; RR, relative risk.

Table 4 Combination versus single-agent chemotherapy in platinum-resistant disease

Study	Agents	Population	PFS	OS
Bolis et al[28]	Paclitaxel		No benefit	No benefit
	Paclitaxel + epirubicin			
Torri et al[29]	Paclitaxel	50% had resistant disease	No benefit	No benefit
	Paclitaxel + doxorubicin			
Buda et al[30]	Paclitaxel	75% had resistant disease	No benefit	No benefit
	Paclitaxel + epirubicin			
Sehouli et al[31]	Topotecan		No benefit	No benefit
	Topotecan + etoposide or gemcitabine			
Monk et al[18]	PLD		No benefit	No benefit
	PLD + trabectedin			
ET43-OVA-301	Weekly paclitaxel		No benefit	No benefit
Lortholary et al[32]	Weekly paclitaxel + carboplatin or weekly topotecan			

Abbreviations: OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

To date, the survival benefits of antiangiogenic agents have been modest, but this success has led to interest in developing more effective ways of combining these agents with standard cytotoxic chemotherapies and with other agents targeting specific signaling pathways in tumor cells. VEGF is a central promoter of the activation phase of angiogenesis in OC. It is also thought to be responsible for malignant ascites and pleural effusions due to microvascular permeability.

Targeting the VEGF ligand

There are two types of VEGF inhibitors: those that neutralize VEGF, such as bevicizumab, and those that block signal transduction of receptors for VEGF and other angiogenic growth factors.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that inhibits VEGF-A. It blocks cancer cells from secreting VEGF and is therefore called an antiangiogenic agent. Table 5 shows three studies of bevacizumab monotherapy in women with recurrent OC and response rates of 15.9%–21% were achieved. Toxicities associated with bevacizumab included hypertension, proteinuria, and wound healing complications.[37–39] Bowel perforations were reported at a rate of 5.4%–11.4%.[39,40]

Table 6 shows the details of bevacizumab use with combination chemotherapy for platinum-sensitive recurrence. OCEANS (The Ovarian Cancer Education Awareness Network) is a positive randomized Phase III trial of 484 women evaluating the addition of biologic therapy (bevacizumab 15 mg/kg q3weeks) to standard doublet chemotherapy using carboplatinum (area under the curve: 4) with gemcitibine 1000 mg/m^2 on days 1 and 8 in recurrent OC until progression.[41] The primary endpoint was PFS. There was a 3.9-month improvement in median PFS (12.3 months versus 8.6 months, hazard ratio [HR] 0.45 [$P < 0.0001$]). There was no OS benefit and there were no new safety concerns identified in this trial. Furthermore, there were no gastrointestinal (GI) perforations; however, it must be acknowledged that women at high risk of GI perforation were excluded from the study. There was a higher incidence of hypertension, proteinuria, and reversible posterior leukoencephalopathy syndrome in the experimental arm.

There is currently a Phase III trial (GOG 213) aiming to enroll 660 women with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer. In this trial, outcomes of those randomized to carboplatin and paclitaxel every 3 weeks will be compared to the chemotherapy regimen with bevacizumab (15 mg/kg) and maintenance bevacizumab every 3 weeks.[42]

AURELIA is a randomized study in which women with platinum-resistant recurrent OC receive either the standard of care (eg, PLD monthly, topotecan weekly, or paclitaxel weekly) or those agents combined with bevacizumab (15 mg/kg q3weeks).[40] Women at high risk for GI perforations were excluded from participation. The women in the experimental arm had a substantially longer PFS (6.7 months versus 3.4 months, HR 0.48; $P < 0.001$) and a higher overall response rate (30.9% versus 12.6%; $P < 0.001$). OS data will be available in 2013 and the safety profile was consistent with prior experience.

VEGF trap

VEGF trap is a fusion protein with extracellular domains of human VEGR-1 and VEGR-2. This protein binds to VEGF-1 and placental growth factor. In a Phase I study of women with

Table 5 Early Phase II studies with bevacizumab in ovarian cancer

Study	Regimen	Patients	Population	ORR	Duration of response (median)	PFS > 6 months
Burger et al[37] GOG 170D	Bev 15 mg/kg q3wk	62	1–2 prior regimens; platinum-sensitive (42%) and resistant (58%)	21% 90% CI: 12.9%–31.3%	10.3 months Median PFS 4.7 months Median OS 17 months	25 pt 40.3% 90% CI: 29.8%–53.6%
Garcia et al[38]	Bev metronomic cyclophosphamide	70	Plat sens (60%) and resistant (40%)	PR 24% 95% CI: 15%–36%	SE-GI fistula in 4	56% 95% CI: 44%–67% PFS platinum-sensitive = 8 months versus platinum-resistant = 5 months $P = 0.004$
Cannistra et al[39]	Bev	44	Platinum-refractory or resistant 2–3 prior regimens	15.9% 95% CI: 7.2%–29%	SE-GI perf 11.4%; 5/44	27.8% PFS median 4 months OS median 11 months

Abbreviations: Bev, bevacizumab; CI, confidence interval; ORR, Overall Response Rate; PFS, progression-free survival; SE, side effects; GI, gastro intestinal; pt, every 3 weeks.

recurrent platinum-resistant OC, VEGF trap given intravenously every 2 weeks resulted in an 11% partial response. The toxicities included grade 3 or 4 hypertension, proteinuria, encephalopathy, and renal failure.[43] VEGF trap has also been studied in a randomized Phase II trial of 55 patients with recurrent symptomatic ascites. Although there was a reduction in the time to repeat paracentesis (55 to 27 days; $P = 0.0019$), there were three intestinal perforations in the VEGF trap arm compared to one in the placebo arm.[44]

Targeting the VEGF receptor

In this section, we focus on small molecular multi-targeted kinase inhibitors that target the VEGF receptor as well as other kinase receptors. The agents listed here are located in the cytoplasmic domain of the cell.

Cediranib

Cediranib (AZD2171) is an oral VEGFR-1, VEGFR-2, VEGFR-3, plasma-derived growth factor receptor (PDGFR)-B, and c-Kit inhibitor. In a Phase II study of women with recurrent or persistent EOC, primary peritoneal, or fallopian tube cancers, daily oral dosing of 45 mg had to be decreased to 30 mg due to toxicity. The response rate in platinum-sensitive patients was 41% and for platinum-resistant disease it was 29%. Toxicity included diarrhea, hypertension, fatigue, and anorexia. Median time to progression was 4.1 months and median OS was 11.9 months.[45] A second study in this patient population showed similar results.[46] A Phase III study with cediranib in platinum-sensitive recurrent EOC comparing platinum/taxane with concurrent and or maintenance cediranib has completed accrual and final results are pending.

BIBF1120

BIBF1120 is a tyrosine kinase inhibitor of VEGF, fibroblast growth factor, and PDGF. When delivered in the maintenance stage of patients with resistant or partially platinum-sensitive disease who have previously responded to chemotherapy, the 36-week PFS rate was 16.3% in the BIBF1120 group and 5% in the placebo group, respectively (HR 0.68, 95% confidence interval [CI] 0.44–1.07, $P = 0.05$; NCT00710762).[47] There was a higher rate of grade 1–2 diarrhea, nausea, and vomiting in the BIBF1120 group. Also, a high rate of grade 3–4 hepatotoxicity (51.2%, as defined by elevated liver enzymes) was seen, but this was rarely clinically significant.[48] A study assessing the addition of BIBF1120 to platinum/taxane first-line therapy has completed and the final results are pending.

Table 6 Platinum-sensitive recurrent EOC

Study	Agents	Number of patients	RR	PFS median	OS median
OCEANS[42]	GC + bev	242	78.5%	12.4 months; HR 0.484 (0.388–0.605) $P < 0.0001$	10.4 months HR 0.534 (0.408–0.698)
	GC + placebo	242	57.4%	8.4 months	7.4 months

Abbreviations: bev, bevacizumab; EOC, epithelial ovarian cancer; GC, gemcitabine and carboplatin; HR, hazard ratio; OCEANS, The Ovarian Cancer Education Awareness Network; OS, overall survival; PFS, progression-free survival; RR, relative risk.

Sorafenib

Sorafenib (BAY 43-9006) is an oral multi-kinase inhibitor that targets the mitogen-activated protein kinase pathway or the Raf/MEK/ERK pathway. It also inhibits VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-B tyrosine kinase activity. A Phase II trial of single-agent sorafenib in persistent or recurrent EOC or primary peritoneal cancer showed that the oral administration of 400 mg twice a day resulted in two partial responders and 20 patients with disease stabilization. Grade 3 and 4 toxicity included rash, GI, cardiovascular, metabolic, and pulmonary side effects.[49] Sorafenib has been evaluated with bevacizumab, but toxicity precluded its continued use.[50] A Phase II study was conducted using sorafenib with gemcitabine. There was one partial response out of 18 evaluable patients and the most frequent grade 3 and 4 toxicities were hematologic hypokalemia, hand–foot syndrome, and fatigue.[51] Sorafenib and gemcitabine in combination with topotecan is being compared to topotecan alone in resistant patients (NCT01047891).[52] It is also being evaluated in platinum-sensitive disease in combination with platinum/taxane (NCT00096200).[53] A randomized Phase II study of sorafenib versus placebo maintenance after complete response to first-line chemotherapy has been completed. The final results of this study are pending.

Sunitinib

Sunitinib (SU11248) is an inhibitor of VEGFR-1, VEGFR-2, PDGFR-A, PDGFR-B, and c-Kit. It has been studied in three Phase II studies in patients with both platinum-sensitive and resistant recurrent OC. Modest activity (8%–17% response rates) was seen in this group of patients.[54–56]

Pazopanib

Pazopanib (GW-786034) is a VEGFR-2 inhibitor. Eleven of 36 patients (31%) had a CA-125 response to pazopanib, with median time to response of 29 days and median response duration of 113 days. The overall response rate was 18% in patients with measurable disease at baseline. The most common adverse events leading to discontinuation of the study drug were grade 3 alanine aminotransferase (8%) and aspartate aminotransferase (8%) elevation. Only one grade 4 toxicity (peripheral edema) was reported.[57] Pazopanib monotherapy was relatively well tolerated, with toxicity similar to other small molecules, oral angiogenesis inhibitors, and demonstrated promising single-agent activity in patients with recurrent OC. Further studies evaluating the potential role of pazopanib in patients with OC are ongoing.[58]

Cabozantanib

The MET pathway has been observed to be overexpressed in advanced OC. Cabozantinib is an oral potent inhibitor of MET and VEGFR2. Results of a randomized Phase II discontinuation trial in 68 patients with recurrent OC given cabozantinib (100 mg orally daily) showed an overall response rate of 24% (18% in platinum-resistant patients and 29% in platinum-sensitive patients).[59] Given these encouraging results, combination studies with chemotherapeutic agents in the recurrent OC are planned.

Targeting angiopoeitin inhibitors

Trabananib

Trabananib (AMG 386) is an investigational peptide-Fc fusion protein that neutralizes the interaction between the Tie2 receptor and angiopoietin-1/2. In a Phase II setting of weekly paclitaxel and high dose weekly intravenous AMB 386 at 10 mg/kg, it was found that patients had a prolonged median PFS of 7.2 months compared to those treated at 3 mg/kg (5.7 months) or placebo (4.6 months).[60] The data suggest evidence of antitumor activity and a dose–response effect, warranting further studies in OC. Two Phase II trials are ongoing comparing trebananib to paclitaxel (TRINOVA-1)[61] or PLD (TRINOVA-2).[62]

Targeting the epidermal growth factor receptor

The EGFR is overexpressed in the majority of EOC and promotes cell proliferation, migration and invasion, angiogenesis, as well as resistance to apoptosis. This makes EGFR an attractive therapeutic target in this disease. A number of strategies to block EGFR activity have been developed,

including monoclonal antibodies blocking ligand binding to the receptor (cetuximab, panitumumab, and matuzumab) and small-molecular-weight tyrosine kinase inhibitors (gefitinib and erlotinib).[63–65] These agents have been evaluated as single agents in recurrent OC, as well as in combination with chemotherapeutic agents in first-line and recurrent settings, and in combination with the antiangiogenic agent bevacizumab in a recurrent setting, as well as in the maintenance stage after completion of first-line chemotherapy. Unfortunately, these treatments have shown only minimal efficacy as single agents and they have not enhanced the effects of chemotherapy or bevacizumab when combined with these agents. Targeting other members of this receptor family (HER-2) with agents such as trastuzumab, pertuzumab, or pan-Erb inhibitors (CI-1033) have not shown any significant antitumor activity in this disease setting.

Imatinib

c-Kit and PDGFR are potential molecular targets in EOC. Imatinib inhibits the kinase domain and subsequent downstream signaling of these receptor tyrosine kinases. Imatinib was administered orally at a dose of 400 mg twice daily in continuous, 28-day cycles with reassessment imaging studies obtained every other cycle. Twenty-three patients were enrolled, including 16 patients who received only 600 mg daily of imatinib because of GI toxicity and fluid accumulation at the starting dose. The median time to disease progression was 2 months (range, 2–14 months). The results of this study indicate that imatinib had minimal activity as a single agent in EOC.[66]

Targeting antifolate receptor agents

Ninety percent of EOCs express the folate receptor alpha (FRA). In fact, FRA is upregulated in the majority of EOCs and is associated with the grade and stage of disease. In contrast, the FRA is absent in normal tissue. The FRA is the primary pathway for folate uptake. Blocking this pathway has been shown to inhibit the growth of FRA-expressing cells in preclinical models. The clinical development of agents targeting this pathway has included monoclonal antibodies to the receptor (farletuzumab) and antibody–drug conjugates (EC-145).[67]

Farletuzumab

Farletuzumab (MORAb-003) is a humanized monoclonal antibody against FRA. In a Phase I dose escalation study, there was no dose-limiting toxicity. This compound has been studied in a Phase II study of platinum-resistant EOC (weekly paclitaxel +/– farletuzumab).[68] After the accrual of 417 of 550 planned patients, this study was terminated in December 2011 at an interim futility analysis. There has been a Phase II efficacy and safety study of farletuzumab with carboplatin and taxane in patients with platinum-sensitive EOC at first relapse. Improved response rate and time to progression was noted when compared to historical controls. Currently, there is an ongoing Phase III study in platinum-sensitive recurrent OC (platinum/taxane ± farletuzumab).[67]

EC145

EC145 is a conjugate of folate and the vinca alkaloid desacetylvinblastine hydrazide (DAVLBH). EC145 binds to the folate receptor delivering DAVLBH into the cell by endocytosis. Encouraging results have been reported from a Phase II study of EC145 in combination with PLD compared to PLD alone.[69] A randomized Phase III trial of PLD (50 mg/m2 q4wk) with and without EC145 (intravenously; days 1, 3, 5, 15, 17, 19, q4weeks) in women with platinum-resistant OC is accruing (NCT01170650).[70] The primary outcome measure will be PFS using RECIST v1.1.

Targeting DNA repair

Poly(ADP-ribose) polymerase (PARP) inhibitors

PARP is an enzyme involved in the repair of single-strand breaks in DNA using the base excision repair pathway.[71] PARP inhibition leads to an accumulation of DNA single-strand breaks and this may lead to DNA double-strand breaks. In normal cells this would be repaired by a recombination DNA repair mechanism, and BRCA 1 and 2 are involved in this process. If there are mutations in the BRCA1 or BRCA2, alternative DNA repair pathways are needed resulting in chromosomal instability and cell death. The use of PARP inhibitors means that there is an accumulation of single- and subsequently double-stranded breaks, and eventually cell death. In total, 5% to 10% of women with OC have a loss of BRCA function. In addition, 50% of women with high-grade serous or undifferentiated carcinoma show loss of BRCA function.[42]

Olaparib

Olaparib (AZD2281) is the most advanced anti-PARP compound in development. Higher doses of olaparib appear to be superior to lower doses. In women with relapsed BRCA-mutated OC, olaparib was used at two doses (400 mg orally administered [PO] every other day compared to 100 mg PO every other day). Median PFS was 5.8 months at the higher dose compared to 1.9 months at the lower dose.[72] In women

with platinum-resistant disease, olaparib 400 mg PO twice a day had a higher response rate (59%) when compared to a low response rate (38%), as the lower dose (200 mg PO twice a day) was similar to the response rate of PLD (39%). PFS curves were similar among the three arms.[73]

Olaparib appears to be beneficial for women with and without BRCA mutations. In platinum-induced partial or complete response platinum-sensitive relapse, a randomized study of olaparib versus placebo in 265 patients showed PFS by RECIST was significantly longer in the olaparib group (HR 0.35, 95% CI 0.25–0.49, $P < 0.00001$, median 8.4 months versus 4.8 months).[74] In 65 women with high-grade serous or undifferentiated OC, olaparib 400 mg every other day showed an objective response in 41% (95% CI 22–64) of those with BRCA 1 or 2 mutations and 24% (95% CI 14–38) without. Olaparib appeared to benefit some women in whom the BRCA status was negative or unknown; however, OS benefit has not been seen. The most common adverse events were fatigue (70%), nausea (66%), vomiting (39%), and decreased appetite (36%).[75]

Another PARP inhibitor, veliparib (ABT-888), is currently being studied in a randomized Phase II trial of ABT-888 + temozolomide versus PLD in women with high-grade serous OC in relapse (NCT01113957).[76]

Other pathways

A number of other pathways that may have relevance to the growth and metastasis of OC have been identified. Many of these are in early phases of development, including agents targeting the PI3 kinase and mTOR pathways (BKM120, GDC-0941, XL147, BEZ-235, GDC-0980, XL765, and GSK 1059615),[42] aurora kinase (ENMD-2076, MLN8237, and MK-0457), polo-like kinase (volasertib), insulin-like growth factor receptor (OSI-906), hedgehog (RG3616, GDC-0440, IPI926), and notch (Ro4929097).

Conclusion

Women with recurrent OC will ultimately die from their disease. The goal in treatment is to prolong the duration of survival while minimizing toxicity and optimizing QOL. An optimal treatment strategy for women with recurrent platinum-refractory/resistant OC does not exist. Given that there is no superior combination of chemotherapy agents for this group, sequential single-agent therapy is usually prescribed based on the side effect profile. The standard of care for women with platinum-sensitive disease is platinum/taxane with or without bevacizumab. Substituting the taxane for another drug like PLD or gemcitabine may offer the woman a treatment with a better toxicity profile. Selected patients with localized disease may benefit from secondary cytoreductive surgery prior to chemotherapy. Angiogenesis inhibitors like bevacizumab, especially when used for this population in a maintenance strategy, have been shown to be beneficial (especially in controlling ascites). Other attractive targets for therapy currently undergoing investigation include PARP inhibitors and antibodies against folinic acid. OC is no longer considered a single disease; rather, each woman's disease presents with unique molecular biology and genetics. As we move into the future, targeted therapies may provide therapeutic options specific to the individual's tumor profile.

Disclosure

The authors report no conflicts of interest in this work.

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