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Targeted treatment of recurrent platinum-resistant ovarian cancer: current and emerging therapies

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Abstract: With advances in surgical techniques and chemotherapeutic agents, mortality rates from epithelial ovarian cancer (EOC) have slightly decreased over the last 30 years. However, EOC still ranks as the most deadly gynecologic cancer with an overall 5-year survival rate of 45%. Prognosis is especially disappointing for women with platinum-resistant disease, where 80% of patients will fail to respond to available therapies. Emerging treatment strategies have subsequently focused on targets which are integral to tumor growth and metastasis. In this review, we will focus on those innovative agents currently under investigation in clinical trials.

Keywords: platinum-resistant, ovarian cancer, targeted therapy, immunotherapy, angiogenesis, growth factors

Introduction

With almost 14,000 deaths expected in 2010, epithelial ovarian cancer (EOC) remains the most lethal gynecologic malignancy.[1] Approximately 75% of women with EOC present with advanced stage disease (stage III or IV).[2] Current management of ovarian cancer at initial presentation typically consists of surgical cytoreduction followed by platinum/taxane combination chemotherapy. While 70% to 80% of patients with advanced EOC will initially respond to this traditional therapy, more than 60% will experience a recurrence of disease and 70% to 90% will ultimately die of their disease.[2] Predictors for recurrence include late stage, residual disease, advanced age, histologic grade, poor performance status, clear cell or mucinous histology, and suboptimal normalization of CA125 levels following first-line therapy.[3,4]

Patients with recurrent EOC are characterized by their initial response to platinum-based therapy.[5] Women who experience recurrences greater than 6 months following a response to platinum-based therapy (ie, platinum-free interval [PFI] >6 months) are characterized as having platinum-sensitive disease.[6] Patients in this category are likely to respond to a platinum-based therapy at the time of relapse and are generally offered a platinum agent or a platinum-containing doublet.[7] Carboplatin-based combination therapy, especially carboplatin with paclitaxel, is most commonly administered as the first-line therapy for recurrence.[8] Alternatively, carboplatin combined with gemcitabine or pegylated liposomal doxorubicin can be used, giving similar response and survival rates.[9,10]

Women who experience recurrences within 6 months following an initial response to platinum-based therapy (ie, PFI < 6 months) or who experience stable disease during platinum-based therapy are characterized as having platinum-resistant ovarian cancer.[6]

This group will often also encompass those individuals who experience disease progression during platinum-based therapy (ie, platinum-refractory).[11] With platinum-resistant disease, the selection of treatment is often made on an individual basis, as treatment for recurrent disease is generally not curable.[12] Goals of treatment often include controlling the disease-related symptoms, limiting treatment-related toxicity, and optimizing quality of life.[13] Patients with platinum-resistant tumors are typically treated with a single cytotoxic agent that is not cross-resistant with platinum compounds; these options will be briefly discussed below.[7]

Current reports indicate a 20% response rate with contemporary agents,[6] emphasizing an absolute need for the development of innovative and effective therapeutic strategies for the management of advanced EOC. In this review we will briefly discuss the traditional chemotherapeutic options for recurrent, platinum-resistant epithelial ovarian cancer and then focus on novel therapeutic strategies currently under investigation.

A MEDLINE search combining the following medical subject terms: "recurrent ovarian cancer, platinum resistant disease and treatment", was performed from 2000 to 2010 in order to identify novel targets for recurrent, platinum-resistant ovarian cancer; only articles written in the English language were included in this review. Ongoing and enrolling clinical trials involving emerging therapeutic agents were subsequently identified by searching the ClinicalTrials.gov registry, abstracts of scientific meetings, and reference lists of included studies. A summary of current clinical trials is presented in Table 1. While the results of many clinical trials are not yet available, we discuss how novel targeted therapies may play a future role in the management of this deadly disease.

Chemotherapy resistance assays

Chemosensitivity and resistance assays, which utilize molecular and cellular strategies with individual tumor biopsies, aim to customize therapy for women with ovarian

Table 1 Current clinical trials involving targeted agents in platinum-resistant epithelial ovarian cancer

Process	Molecular target	Agent	Trial phase	Additional agents	ClinicalTrials.gov identifier
Anti-tumor immunity	MUC1	MUC1-KLH vaccine	I	Adjuvant QS21	NCT00006041
Anti-tumor immunity	Whole tumor cell	Dendritic cells	II	Ontak	NCT00703105
			I	Bevacizumab/cyclophosphamide	NCT00683241
			0	Daclizumab/bevacizumab	NCT01132014
Anti-tumor immunity	Whole tumor cell	Adoptive transfer of T lymphocytes	I/II	tumor lysate-pulsed dendritic cells	NCT00603460
Angiogenesis	VEGF	Bevacizumab	III	Paclitaxel/topotecan/PLD	NCT00976911
			II	Gemcitabine	NCT01131039
			II	PLD	NCT00846612
			II	PLD	NCT00945139
			II	Abraxane	NCT00407563
Angiogenesis	VEGFR-2	Ramucirumab	II	N/A	NCT00721162
Angiogenesis	VEGF	Aflibercept (VEGF Trap)	I/II	Docetaxel	NCT00436501
Angiogenesis	VEGFR2	Cediranib	III	Carboplatin/paclitaxel	NCT00544973
Angiogenesis	VEGFR2	Vandetanib	I/II	PLD	NCT00862836
Cellular proliferation	EGFR		II	Docetaxel	NCT 00872989
Angiogenesis Cellular proliferation	EGFR	Panitumumab	II	PLD	NCT00861120
Angiogenesis	EGFR	Erlotinib	II	Topotecan	NCT01003938
Cellular proliferation			II	Bevacizumab	NCT00126542
			II	Bevacizumab	NCT00696670
Angiogenesis	VEGFR PDGFR C-Kit	Sorafenib	II	Topotecan	NCT01047891
			II	Gemcitabine	NCT00096395
Angiogenesis	PDGFRα	IMC3G3	II	PLD	NCT00913835
Folate metabolism	FRα	MORAb-003	II	Paclitaxel	NCT00738699
DNA repair	PARP	Veliparib	I	PLD	NCT01145430
DNA repair	PARP	Iniparib	II	Gemcitabine	NCT01033292

Abbreviations: MUC1, mucin 1; VEGF, vascular endothelial growth factor; PLD, pegylated liposomal doxorubicin; VEGFR-2, vascular endothelial growth factor receptor 2; N/A, not applicable; EGFR, epidermal growth factor receptor; PDGFRα, platelet derived endothelial growth factor receptor alpha; FRα, folate receptor alpha; PARP, poly-ADP-ribose polymerase.

cancer, especially those with recurrent disease. The utility of a chemosensitivity assay in recurrent disease was examined in a prospective randomized control trial of 180 women with platinum-resistant disease.[14] Response rates (40.5% vs 31.5%) and median progression-free survival (104 vs 93 days) were greater in women randomized to the sensitivity assay-directed group compared with the physician's choice arm. While overall survival was similar between groups, the authors suggest that chemosensitivity testing may provide useful information in select patients. Several national organizations, including the American Society of Clinical Oncology, have released statements to help direct clinical use of these assays; at this time, there are not enough reliable data to recommend the use of these assays in clinical practice.[15] Future studies focusing on the utility and cost benefits of these assays in platinum-resistant disease may help to clarify their impact on patients' outcomes.

Chemotherapy use in platinum-resistant disease

Nonplatinum-based single-agent chemotherapy is considered first-line therapy in the treatment of recurrent, platinum-resistant EOC. Commonly utilized agents include pegylated liposomal doxorubicin, paclitaxel, gemcitabine, topotecan, docetaxel, and etoposide, with response rates ranging from 10% to 30%.[6] Often the choice of agent is driven by its side effect profile, administration, and availability.

Pegylated liposomal doxorubicin (PLD), a DNA intercalating agent with reported objective response rates (ORRs) as high as 26%, is commonly administered as the first-choice nonplatinum reagent for recurrent platinum-resistant disease.[16,17] Due to its adverse events, the most significant of which is palmar-plantar erythrodysesthesia (hand–foot syndrome), PLD is currently being evaluated as a component of combination therapy.[18]

Paclitaxel, a microtubule inhibitor, has produced ORRs up to 30% in women with platinum-resistant EOC,[5] and combination paclitaxel and carboplatin therapy has also demonstrated objective clinical benefits.[19] Common adverse events with paclitaxel include neurotoxicity and myelosuppression, events that can be potentially improved with different dosing schedules. Through a similar mechanism, docetaxel has demonstrated activity in cases of platinum-resistant disease but with reduced efficacy and increased patient toxicity.[20]

Single-agent gemcitabine, a nucleoside pyrimidine analog, has a reported ORR of 16% in platinum- and paclitaxel-refractory disease.[21] While myelosuppression is a common dose-limiting toxicity, gemcitabine may be an acceptable alternative to PLD given similar response rates and progression-free survival in a recent phase III study.[22]

Topoisomerase inhibitors utilized in platinum-resistant patients include topotecan and etoposide. While respective response rates of 12% to 14%[23] and 26.8%[24] with topotecan have been reported, dosing is limited by hematotoxicity. In a phase II Gynecologic Oncology Group (GOG) study, Rose et al reported a response rate of 32% with etoposide in platinum and paclitaxel resistant patients.[25]

Second-line agents for platinum-resistant disease include irinotecan, vinorelbine, ifosfamide, and leucovorin-modulated 5-fluorouracil. In a single-institution phase II trial, irinotecan, a topoisomerase inhibitor, produced a response rate of 17.2% in 31 patients with platinum-resistant/refractory EOC or primary peritoneal cancer (PPC) with acceptable toxicity.[26] Vinorelbine, an antimicrotubule agent, has demonstrated a response rate of 21% in a recent phase II trial.[27] Ifosfamide, an alkylating agent, produced a response rate of 12% in a phase II trial of 41 patients with platinum-resistant disease, the most common reported toxicities including myelosuppression, nephrotoxicity, and central nervous dysfunction.[28] 5-Fluorouracil, a pyrimidine analog, although well tolerated, produced a response rate of only 18% in a recent retrospective report.[29]

Novel cytotoxic therapies

Emerging cytotoxic agents are currently being introduced into the management of platinum-resistant ovarian cancer. These include chemotherapeutic compounds classified in drug categories with known activity in EOC, including taxanes (eg, paclitaxel poliglumex), anthracyclines (eg, sabarubicin), alkylating agents (eg, canfosfamide), and topoisomerase inhibitors (eg, rubitecan), or novel drug categories, such as epothilones (eg, ixabepilone, patupilone).

Ixabepilone belongs to a new class of agents, epothilones, which act to stabilize microtubules. While mechanistically similar to taxanes, epothilones are structurally unrelated and may circumvent mechanisms in taxane resistance.[30] In a phase II GOG trial, ixabepilone produced an ORR of 14.3% in 49 women with platinum- and taxane-resistant EOC or PPC.[31] Clinical trials with ixabepilone monotherapy (NCT00025155, NCT00030706) and combination therapy with pegylated liposomal doxorubicin (NCT00182767) are currently accruing.

Trabectedin is an anti-tumor agent which binds to DNA and interferes with DNA repair, thereby blocking cell cycle progression.[32] In a multicenter phase II trial, trabectedin monotherapy was active in platinum-resistant EOC with

an ORR of 6.3%.[33] Trabectedin in combination with PLD was recently evaluated in a randomized phase III trial with platinum-sensitive and -resistant recurrent disease.[18] While the response rate was significantly higher in women with platinum-sensitive disease receiving combination therapy vs PLD monotherapy (35.3% vs 22.6%, $P = 0.004$), ORRs were not statistically different between treatment arms in the platinum-resistant population.

Pemetrexed is a folate antimetabolite which inhibits a number of enzymes critical to nucleotide synthesis.[34] In a phase II GOG trial, pemetrexed monotherapy was administered to 48 women with platinum-resistant EOC or PPC, reporting an ORR of 21% with median progression-free and overall survivals of 2.9 months and 11.4 months, respectively.[35]

Phenoxodiol promotes Fas-mediated apoptosis by activating the mitochondrial caspase system, inhibiting the X-linked inhibitor of apoptosis and disrupting FLICE inhibitory protein (FLIP) expression.[36] In vitro and preclinical animal studies indicate that phenoxodiol can sensitize EOC cells to carboplatin, paclitaxel, and gemcitabine,[37] and phenoxodiol combination therapies including carboplatin, paclitaxel, and docetaxel are currently being evaluated.

Third-generation platinum agents, including oxaliplatin, satraplatin, and picoplatin, have incomplete cross-resistance with either cisplatin or carboplatin and have subsequently been shown to have minor activity in platinum-resistant disease. In a phase II GOG trial, single-agent oxaliplatin produced an ORR of 4.3% in 23 women with platinum-resistant or -refractory EOC,[38] which has led to investigation of oxaliplatin in combination with 5-fluoruracil/leucovorin,[39] paclitaxel,[40] PLD,[41] and gemcitabine.[42] Satraplatin is an orally administered platinum agent with in vitro activity against platinum-resistant ovarian cancer cell lines;[43] however, these findings have not yet been confirmed in clinical trials. Picoplatin is currently under investigation in a phase I trial of patients with advanced solid tumors, including ovarian cancer (NCT00465725).

Emerging approaches to platinum-resistant EOC

In addition to novel cytotoxic agents, targeted molecular strategies have been employed in the treatment of recurrent, platinum-resistant ovarian cancer. These strategies attempt to manipulate processes critical to ovarian carcinogenesis, including cellular growth and proliferation, cellular adhesion, intracellular signaling pathways, angiogenesis, and DNA repair pathways.[44] In the following section, we will focus on emerging agents targeting host-tumor immune responses, intracellular signaling pathways, cellular adhesion molecules, endocrine pathways, and DNA repair mechanisms.

Immunotherapy

Effective host anti-tumor immune responses have the potential to influence prognosis in patients with EOC. The presence of tumor-infiltrating lymphocytes (TILs) has been correlated with significantly improved progression-free and overall survival rates in women with advanced stage EOC.[45] Further, the presence of CD4+CD25+FOXP3+ T regulatory (Treg) cells in tumors has a reported negative impact on survival, suggesting that these cells might suppress host anti-tumor immunity.[46,47] Thus, by manipulating the host immune system, it may be possible to enhance host anti-tumor immune responses and improve patient outcomes, especially in those with platinum-resistant disease. Current immunotherapeutic approaches employ either vaccines based on tumor-associated antigens (TAA), antitumor cytokines, or antibodies targeting co-stimulatory and immunosuppressive molecules.[48]

Tumor antigens

Several proteins that are abnormally expressed in cancer cells, due to mutations, overexpression, or post-translational modifications, have been identified and are currently studied as targets for immunotherapy. In a recent analysis from the National Cancer Institute Pilot Project for the acceleration of translational research, 75 tumor antigens were priority ranked for cancer vaccine development.[49] Some of these antigens, including MUC1, CA125, human epidermal growth factor receptor 2 (HER2)/neu, membrane folate receptor, TAG-72, mesothelin, and NY-ESO-1, are targets of therapeutic tumor vaccines in ovarian cancer.[48]

Due to its oncogenic properties, immunogenicity and expression pattern, MUC1 received the second highest priority ranking, after WT1.[49] MUC1 is a transmembrane mucin overexpressed in more than 90% of epithelial ovarian cancers, including platinum-resistant tumors.[50,51] Thus, MUC1 has been often studied as a target for antibody-based immunotherapy. A phase I trial using a murine anti-MUC1 antibody (HMFG1) was conducted in 26 patients with persistent/recurrent ovarian cancer following platinum-based chemotherapy.[51] While no clinical responses were appreciated, anti-HMFG1 and anti-MUC1 antibody responses were significantly elevated in those individuals completing the vaccination regimen. In a phase I/II trial, 52 women received intraperitoneal (IP) injections of a radioactively-labeled

form of this antibody, yttrium-90-muHMFG1, following traditional surgery and platinum-based chemotherapy with improved median survival rates compared with historical controls.[50] While a subsequent phase III trial failed to show a survival benefit with IP administration of yttrium-90-muHMFG1 as consolidation treatment, the authors reported a significant decrease in IP recurrences in the treatment group.[52] Unfortunately, this finding was offset by increased extraperitoneal recurrences. In addition to MUC1-specific antibodies, vaccines based on MUC1 peptides designed to trigger T cell immunity have been proposed in ovarian cancer (NCT00006041).

CA125 (MUC16), another member of the mucin family, is a marker utilized to monitor response to chemotherapy and to survey for disease recurrence. Approximately 80% of ovarian cancer tumors are CA125 positive, suggesting that immunotherapy targeting this TAA may be of clinical relevance.[53] Monoclonal antibodies to CA125 (B43.13, oregovomab) have been utilized in phase II and III trials of patients with recurrent disease.[53,54] In the first trial, oregovomab was administered to 13 heavily pretreated, recurrent ovarian cancer patients, including 6 women with platinum-resistant disease.[53] Oregovomab and CA125 antibody and T cell specific responses were reported in greater than 50% of the patients. While there were no objective responses, 23% of patients experienced stabilization of disease and survival greater than 2 years, and these clinical responses corresponded with robust immune responses to treatment.[53] In the latter trial, 20 patients with advanced recurrent ovarian cancer (and with a history of platinum exposure) received oregovomab followed by optional chemotherapy.[54] Anti-CA125 antibodies were produced in 2 (11%) patients, while 15 (79%) of patients developed human anti-mouse antibodies (HAMAs) and anti-oregovomab antibodies. Overall median survival and progression-free survival was 70.4 weeks (4.6 to 14.6 weeks) and 11 weeks (2.6 to 114.6 weeks), respectively. T cell responses specific to CA125 and/or autologous tumor were significantly associated with improved survival ($P = 0.002$).

Anti-idiotypic antibodies to CA125 (ACA125, abagovomab) have also been utilized in clinical trials.[55,56] Generated against primary anti-CA125 antibodies, these antibodies can serve as surrogate antigens given that they imitate the antigen of interest, and it has been postulated that vaccination with anti-idiotypic antibodies can increase host responses.[48] In a phase I/II trial, abagovomab was administered to 119 patients with advanced ovarian cancer, including 44 patients with platinum-resistant disease.[56] Antibodies to ACA125 and CA125

were generated in 68% and 50% of patients, respectively, and antibody-dependent cell-mediated cytotoxicity (ADCC) of CA125-positive cancer cells was demonstrated in 27% of patients. Individuals with anti-ACA125 antibodies had a significantly longer survival compared to those without such a response (median, 23.4 months vs 4.9 months; $P < 0.0001$). Two additional studies demonstrated the presence of anti-abagovomab antibodies in all evaluable patients, but these responses were not assessed for association with survival benefit due to study design.[55,57]

Cytokine therapy

Proinflammatory cytokines, including interleukins (IL) 2, 4, 7, 12 and 18, interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and granulocyte-macrophase colony-stimulating factor (GM-CSF), have been utilized in preclinical models to induce anti-tumor immune responses.[58] In a phase II trial in patients with platinum-resistant and refractory EOC, IP IL-2 therapy resulted in an overall response rate of 25% with a median survival time of 2.1 years.[59] The authors also reported a significant association between patient survival and changes in CD3 T cells and IFN-γ producing CD8 T cell counts at early treatment time points, suggesting that anti-tumor responses may be critical to prognosis.

GM-CSF alone and in combination with recombinant IFN-γ 1b (rIFN-γ 1b) has recently been incorporated into phase II trials.[60,61] Roche et al used single agent GM-CSF in 72 women with asymptomatic recurrent müllerian malignancy without an indication for immediate systemic chemotherapy.[60] While 1 patient experienced a complete response and 20 patients experienced stable disease following treatment, 70% of women experienced a drop in CA125 levels from baseline. GM-CSF in combination with rIFN-γ 1b and carboplatin produced a response rate of 56% in a cohort of 59 patients with recurrent, platinum-sensitive ovarian, fallopian tube and PPC.[61] Given these encouraging results, further studies examining efficacy in platinum-resistant disease are necessary.

IFN-γ induced upregulation of major histocompatibility complex molecular expression on antigen presenting cells, including dendritic cells, macrophages and B cells, can enhance host immune responses via activation of T cell-mediated pathways.[62] Preclinical evaluation of a CD80 (B7-1)/IFN-γ modified vaccine showed enhancement of tumor-specific cytotoxic activity, resulting in reduction of tumor growth.[63] However, this vaccine has not yet been attempted in clinical trials with platinum-resistant disease.

Other immune strategies

In addition to TAA and recombinant cytokine therapies mentioned above, vaccine-approaches in EOC have also utilized whole tumor cell lysates and dendritic cells in an attempt to boost host anti-tumor immune responses. The former affords the opportunity for broad tumor antigen exposure, while use of dendritic cells (DCs) enhances anti-tumor immunity via specific tumor-antigen presentation and activation of effector T cells.[44] The first and currently only Food and Drug Administration approved cancer therapeutic vaccine is the DC-based Provenge® vaccine (Dendreon Corporation, Seattle, WA) administered as autologous cellular therapy in castrate-resistant prostate cancer.[64] The value of Provenge in triggering effective immunity against other cancer types, including ovarian cancer, remains to be established.

DC-based immunotherapy in ovarian cancer has focused on several approaches, including exposure (also known as pulsing) of DCs to whole cell tumor lysates, defined ovarian tumor peptides, and ovarian tumor cells, to induce a cytotoxic T lymphocyte (CTL) response.[65] In a pilot study, autologous DCs were pulsed with HER-2/neu or MUC1-derived peptides and administered to 10 patients with advanced breast or ovarian cancer.[66] Half of the patients experienced peptide-specific CTL responses, but unfortunately these responses were not correlated with long-term outcomes. In a phase I trial, autologous tumor antigen-pulsed DCs were administered to 6 patients with progressive or recurrent ovarian cancer.[67] Half of the patients experienced stabilization of disease with progression-free intervals of 8 to 45 months, and lymphoproliferative responses were reported in 2 patients. Given these promising data, DC-based immunotherapy is currently the focus of several new trials (NCT00703105, NCT00683241, and NCT01132014) which will hopefully demonstrate an impact on long-term prognosis.

Adoptive immunity is a process by which immune cells, including T lymphocytes, B lymphocytes, natural killer cells, and macrophages, are removed from an individual, modified extracorporeally and then placed back into the same individual.[68] The adoptive transfer of autologous TILs has proven to be quite effective in metastatic melanoma patients, with reported ORRs of greater than 50%.[69] The same process was met with high response rates in a sample of women with advanced or recurrent EOC,[70] and subsequent studies in ovarian cancer have examined the utility of adoptive transfer with modified T cells to enhance antitumor activity.[71,72] A phase I/II trial has been proposed in which patients with recurrent EOC or PPC will undergo adoptive transfer of ex vivo CD3/CD28-costimulated autologous peripheral blood T cells

along with tumor lysate-pulsed DCs (DCVax®-L; Northwest Biotherapeutics, Inc., Bethesda, MD) (NCT00603460) in order to determine the feasibility and safety of this combination and progression-free survival at 6 months.

In addition, investigations have begun focusing on molecules (eg, cytotoxic T lymphocyte-associated antigen 4, CTLA-4)[73] and cell populations (Tregs)[74] which suppress host immune responses. These trials will hopefully reinforce the utility of these novel immunotherapeutic techniques in the treatment of recurrent EOC and lay the foundation for studies specific to platinum-resistant disease.

Tyrosine kinase receptors and intracellular signaling pathways

Angiogenesis is critical to tumor growth/metastasis and several proangiogenic factors, including vascular endothelial growth factor (VEGF), IL-8, platelet-derived endothelial cell growth factor (PDGF), angiogenin, and fibroblast growth factor (FGF), have been implicated in tumorigenesis.[75] Molecules, including VEGF, epidermal growth factor receptor (EGFR), and PDGF among numerous others, play critical roles in processes that support cancer growth and metastasis, and several tyrosine kinase receptors and intracellular signaling pathways are currently under review for ovarian cancer targeted therapy. Of these molecules, VEGF has been the most commonly studied, given that it is abundantly present in the serum of patients with EOC,[76,77] and that elevated VEGF levels have been associated with poor survival.[78]

Bevacizumab is a humanized monoclonal antibody which interferes with the binding of VEGF-A to its receptor. Bevacizumab has been utilized as monotherapy or in combination in several clinical trials, where its efficacy and safety have been demonstrated.[79,80] GOG-170D was a phase II trial in which single-agent bevacizumab was administered intravenously to 62 women with persistent or recurrent EOC or PPC (41.9% with platinum-resistant disease) to assess efficacy and tolerability.[79] Clinical responses were observed in 21% of patients, and median progression-free and overall survivals were 4.7 and 17 months, respectively. Bevacizumab was well tolerated in this sample, suggesting it may serve as an effective second- or third-line option for patients with EOC/PPC.

Cannistra et al investigated the use of bevacizumab monotherapy in a sample of 44 women with platinum-resistant EOC or PPC who had experienced disease progression during or within 3 months of discontinuing topotecan or liposomal doxorubicin.[80] Seven patients (15.9%) experienced partial responses; median progression-free and overall survival

were 4.4 and 10.7 months, respectively, at study conclusion. However, enrollment was closed early in this study due to a higher than expected rate of gastrointestinal perforation (GIP, 11.4%). GIP was significantly associated with increased number of prior chemotherapy regimens, suggesting this adverse event may be due to the advanced disease status in this patient sample. This study suggests that bevacizumab monotherapy may play a role in the treatment of patients with heavily pretreated, platinum-resistant EOC although further prospective evaluation is warranted.

Bevacizumab in combination with taxanes and cyclophosphamide has also been investigated in women with recurrent EOC.[81,82] In a phase II trial evaluating bevacizumab and cyclophosphamide therapy in 70 patients, 24% of patients experienced a partial response to therapy and median progression-free and overall survival were 7.2 and 16.9 months respectively.[82] The results of a recently completed phase II trial of weekly topotecan with bevacizumab in women with platinum-resistant EOC, fallopian tube cancer, or PPC (NCT00343044) are also currently pending. Other bevacizumab combination regimens including paclitaxel, topotecan, or liposomal doxorubicin (NCT00976911, NCT01131039, NCT00846612, NCT00945139, NCT00407563) are currently in the evaluation process. The results of these trials will certainly generate considerable interest and may potentially impact treatment for recurrent, platinum-resistant disease.

Ramucirumab (IMC-1121B), which blocks VEGFR-2 on tumor endothelial cells, is another human monoclonal antibody targeting the VEGF pathway.[83] The safety and tolerability of this antibody have been demonstrated by a near-completed phase I trial,[83] while a nonrandomized phase II trial (NCT00721162) is investigating ramucirumab monotherapy in platinum-refractory persistent or recurrent EOC, PPC, or fallopian tube cancer to assess efficacy.[84]

VEGF Trap (aflibercept) is a recombinant fusion protein which combines the VEGF binding domains of VEGFR1 and VEGFR2 with the Fc region of immunoglobulin (IgG1) and acts as a soluble decoy receptor by binding to VEGF.[85] In a randomized phase II trial, 11% of patients with recurrent, platinum-resistant disease achieved objective responses with VEGF Trap,[86] and VEGF Trap combined with docetaxel is currently under investigation in a phase I/II trial of patients with persistent or recurrent EOC, PPC, or fallopian tube cancer (NCT00436501).

Small molecule receptor tyrosine kinase inhibitors (TKIs) targeting the VEGF pathway are also being examined. Cediranib, a competitive inhibitor of VEGFR2, is currently under investigation in the ICON 6 trial. In this randomized,

phase III trial, cediranib with carboplatin/paclitaxel chemotherapy is being compared to carboplatin/paclitaxel alone in a sample of women with recurrent, mostly platinum-sensitive, EOC utilizing overall survival as the primary end point.[87] Vandetanib is another TKI which interferes with both VEGFR2 and EGFR, resulting in its antiangiogenesis and antiproliferative activity. Combination regimens with vandetanib and liposomal doxorubicin (NCT00862836) and docetaxel (NCT 00872989) are currently under investigation in phase I and/or II trials.

EGFR (ErbB1, HER1), ErbB2 (HER2), ErbB3, and ErbB4 are 4 tyrosine kinase receptors which comprise the EGFR receptor family.[88] Following ligand binding, these receptors undergo dimerization, internalization of the ligand-receptor complex, and finally tyrosine auto-phosphorylation.[85] Via downstream targets such as PI3K/Akt and MAPK, activation of EGFR receptors ultimately leads to cellular proliferation, differentiation, metastasis, and angiogenesis.[89] As a result, monoclonal antibodies have been created to inhibit these EGFR-dependent pathways, most notably EGFR and ErbB2 (HER2). Cetuximab and panitumumab are mouse/human chimeric and human monoclonal antibodies, respectively, which target EGFR. Trastuzumab and pertuzumab are monoclonal antibodies which target ErbB2/HER2.

In a phase II trial, cetuximab monotherapy was administered to 25 women with persistent or recurrent EOC or PPC (64% with platinum-resistant disease) in order to determine its safety and efficacy.[90] Only 1 patient (4%) with platinum-resistant EOC experienced an objective partial response; this trial was subsequently terminated due to poor response rate. While all patient tumors expressed EGFR, the authors postulated that future investigation should focus on determining which subcohort of patients would directly benefit from therapy. Panitumumab is a monoclonal antibody which has been studied in EGFR-expressing metastatic colorectal cancer.[91] Panitumumab in combination with PLD is currently under investigation in a phase II trial with platinum-resistant, KRAS wild-type EOC patients (NCT00861120).

After demonstrating the ability to prolong disease-free and overall survival in breast cancer, trastuzamab, a monoclonal antibody that interferes with the HER2 receptor, has been approved for use as an adjuvant therapy in patients with HER2-positive breast cancer.[92] HER2 expression is negatively correlated to survival in ovarian cancer patients.[93] In a phase II GOG trial, trastuzumab was administered as a single agent to 41 women with HER2-positive, recurrent, or persistent EOC or PPC.[94] There was an overall response rate of 7.3% with a median progression-free survival of

2.0 months, suggesting that the overall potential therapeutic benefit for trastuzamab in EOC may be limited.

Pertuzumab, a monoclonal antibody referred to as a "HER dimerization inhibitor", is currently being evaluated in patients with HER2-positive EOC due to the ability to prevent activation of HER2 downstream pathways.[85] In a randomized controlled phase II trial of 130 women with platinum-resistant EOC/fallopian tube cancer/PPC, women who had received pertuzumab and gemcitabine had better ORRs (13.8% vs 4.6% for placebo group) and a trend towards improved progression-free survival (hazard ratio 0.66, $P = 0.07$) when compared to a sample receiving gemcitabine and placebo.[95] While these findings were nonsignificant, the authors suggest that with further study pertuzumab may be an effective agent for the treatment of platinum-resistant disease.

TKIs targeting the EGFR family, including gefitinib and erlotinib, are currently under evaluation. In a phase II GOG trial, gefitinib was administered to a group of 27 women with recurrent or persistent EOC or PPC, consisting of 37% and 63% with platinum-sensitive and -resistant disease, respectively.[96] Only 1 patient (4%) experienced an objective response to treatment; however, women in this trial were not prescreened for EGFR mutations which the authors argue may improve response rates to gefitinib. These results were further substantiated in a phase II trial in which there were no objective responses to gefitinib monotherapy in women with heavily pretreated, recurrent EOC who had detectable levels of EGFR (both total and a phosphorylated form).[97] In a recent phase II trial, erlotinib and carboplatin combination therapy was more active in sensitive than -resistant disease.[98] Trials combining erlotinib with topotecan (NCT01003938) and with bevacizumab (NCT00126542, NCT00696670) are currently under way.

In addition to EGFR, investigations have focused on other growth factor receptors critical to the angiogenesis pathway. Platelet-derived growth factor receptor (PDGFR), a tyrosine kinase receptor which enhances cellular proliferation, is present in 50% to 80% of ovarian cancers.[99] TKIs targeting PDGFR, including imatinib, sorafenib, sunitinib, and pazopanib, are presently under review in recurrent EOC. Imatinib, a TKI with activity against Abl, PDGFR, and c-kit, has minimal activity in platinum-resistant disease, as highlighted by 2 recent phase II trials.[100,101] Sorafenib, which targets VEGFR, PDGFR, and c-kit, is currently being examined in combination with topotecan (NCT01047891) and gemcitabine (NCT00096395). Treatment with sunitinib, which targets VEGFR and PDGFR, produced no objective responses in a phase II trial of women with recurrent ovarian

cancer.[102] Pazopanib, a TKI targeting VEGFR, PDGFR, and c-kit, has produced an ORR of 18% in a phase II trial with 36 recurrent EOC patients, including 9 with platinum-refractory and -resistant disease.[103] In addition to small molecule TKIs, a monoclonal antibody, IMC 3G3, has been introduced which inhibits the PDGFRα; this antibody combined with PLD is currently under review in a phase II trial of platinum-resistant EOC patients (NCT00913835).

Aurora kinases and members of the hedgehog and PI3K/AKT/mTOR signaling pathways have also been examined as novel targets for recurrent EOC therapy; the results of several phase II trials involving these agents are currently pending.

Folate metabolism

Folate receptor-alpha (FRα) is a glycosyl-phosphatidylinositol-linked member of the folate receptor family which is overexpressed in the majority of nonmucinous EOCs.[104,105] FRα binds folic acid with high affinity, permitting cancer cells to grow in low folate concentrations and thereby facilitating DNA synthesis.[106] Three anti-human FRα monoclonal antibodies have been studied in clinical trials: MOV18, murine LK26 and MORAb-003. MOV18 is a murine or chimeric anti-FR monoclonal antibody which had been administered to women with ovarian cancer in phase I trials and suggested a clinical benefit with minimal toxicity.[107,108] More recently, this antibody has been investigated in radio-immunotherapy preclinical studies.[109,110] LK26 is another murine anti-FR antibody which had been investigated in preclinical trials but was never studied in clinical trials due to its decreased affinity for the FR following humanization of the antibody.[111] MORAb-003, a humanized anti-FR monoclonal antibody, was subsequently derived by optimizing the LK26 molecule. MORAb-003 has been studied in phase I and II trials;[112,113] preliminary results suggest that this molecule is safe and efficacious in the treatment of EOC. The utility of this molecule in treating platinum-resistant disease will hopefully be determined by a randomized, double-blinded, placebo-control study examining paclitaxel with and without concurrent MORAb-003 (NCT00738699).

Cellular adhesion

Cellular adhesion molecules, including epithelial cell-adhesion molecule (EpCAM), mesothelin, and integrin, may play critical roles in tumor metastasis and are currently molecular targets in recurrent EOC. EpCAM is an antigen expressed in the majority of epithelial cancers,[114] and is significantly overexpressed in recurrent EOC when

compared with normal ovarian tissue and with primary ovarian carcinomas.[115] Further, EpCAM is highly expressed on the surface of chemotherapy-resistant ovarian cancer cell lines.[115] EpCAM is thus a molecule which can facilitate targeted immunotherapy in the local tumor microenvironment, especially for those women with recurrent and chemotherapy resistant disease. Catumaxomab is a trifunctional antibody with 2 antigen-binding sites, targeting EpCAM on epithelial tumor cells and CD3 on T cells, with a functional Fc domain.[116] Thus, this antibody functions to recruit and activate immune effector cells at the tumor site. In a randomized, 2-arm phase II/III trial, IP catumaxomab in combination with paracentesis was compared with paracentesis alone in 258 patients with recurrent, symptomatic malignant ascites, including 129 patients with primary ovarian cancer.[117] In the ovarian cancer patients, median puncture-free survival and time to next paracentesis were both significantly prolonged in the combination group compared with the paracentesis alone group, suggesting that catumaxomab provides a clinical benefit to those women with EOC-related malignant ascites.

Mesothelin is overexpressed on ovarian cancer cell membranes and is believed to be involved in cellular adhesion.[118] An anti-mesothelin immunotoxin, SS1P, has recently been examined in phase I trials of mesothelin-expressing tumors and while clinical activity has been suggested, these findings need to be further confirmed.[118] Integrins are receptors that are important in cellular adhesion; a monoclonal antibody to alpha(v)-integrins is currently under investigation in phase I trials.

Hormonal therapy

Hormones, particularly estrogen and progesterone, play key roles in ovarian carcinogenesis. This association is probably best highlighted by the fact that oral contraceptive pill use decreases the incidence of ovarian cancer.[119] Further, estrogen and progesterone receptors are often present on ovarian cancer cells, and in vitro responses have been reported to tamoxifen and other hormonal agents.[120] Unlike in breast cancer, hormone-driven therapy has not been met with success in the treatment of platinum-resistant EOC.

Selective estrogen receptor modulators, specifically tamoxifen, have been investigated in the treatment of platinum-resistant disease. In a recent Cochrane review, the role of tamoxifen in recurrent EOC could not be established due to a lack of comparative studies.[121] However, when analyzing noncomparative studies, an overall ORR of 9.6% was determined, with individual studies reporting ranges from 0% to 56%. Aromatase inhibitors inhibit the

conversion of androgens into estrogens via the aromatase enzyme. These agents, particularly letrozole, have also been studied in the treatment of platinum-resistant EOC. In a single-institution, phase II trial, letrozole produced an ORR of 3% in a sample of patients with platinum- and taxane-resistant, estrogen-receptor positive recurrent EOC or PPC and 74% of patients experienced disease progression.[122] Furthermore, an ORR of 9% was appreciated in a sample of 42 women with estrogen-positive relapsed EOC, of which 43% of individuals had platinum-resistant disease.[123] Fulvestrant is a novel estrogen receptor antagonist which does not possess any agonistic effects. In a single-institution, phase II trial, fulvestrant produced no objective responses by modified RECIST criteria in a sample of 26 heavily pretreated EOC patients but did stabilize disease in 35% of patients.[124] No further studies are currently available which focus on the use of this agent specifically in platinum-resistant disease. Mifepristone is a competitive progesterone receptor antagonist which has recently been studied in platinum-resistant EOC. In a phase II GOG trial, mifepristone was administered to patients with recurrent or persistent EOC, fallopian tube cancer, or PPC.[125] While it is unclear how many patients had platinum-resistant disease, only 1 patient experienced an objective response, suggesting that this agent is likely not effective in this patient sample. No additional studies have been reported. GnRH analogs have also been investigated in platinum-resistant EOC. In a sample of 12 patients with platinum-resistant disease, leuprolide produced an ORR of 8.3%; however, 66.7% patients experienced disease progression.[126] In a nonrandomized, phase II trial, goserelin in combination with tamoxifen was administered to 26 patients with recurrent EOC, including 65% with platinum-resistant disease.[127] While authors suggest that 50% of patients experienced a clinical benefit, objective responses were experienced in only 3 patients (11.5%). A luteinizing hormone-releasing hormone antagonist, cetrorelix, has also been shown to modest activity in a cohort of patients with platinum-resistant disease.[128]

DNA repair pathways

BRCA 1 and 2 are two proteins that play critical roles in homologous recombination, a process that repairs double-stranded DNA breaks.[129] Germline mutations in BRCA 1 and 2 are present in up to 15% of women afflicted with ovarian cancer.[130] Inhibition of an additional DNA repair pathway, specifically base excision repair (BER), has been shown to be a lethal event in BRCA dysfunctional cells, a term commonly referred to as synthetic lethality.[131]

Poly-ADP-ribose polymerase (PARP) is a nuclear enzyme which participates in BER and has been a current target of therapy in BRCA dysfunctional patients. While initial investigation has focused on the use of PARP inhibitors in individuals with germline mutations, a recent report suggests that additional EOC patients with somatic BRCA 1 or 2 dysfunction, a phenotype referred to as "BRCAness", may also benefit from this novel drug class.[132] Olaparib is the most studied PARP inhibitor in women with EOC. In a multicenter, international phase II trial, 100 mg and 400 mg doses of olaparib were administered to women with BRCA 1 or 2 germline mutations who had recurrent EOC, fallopian tube cancer, or PPC;[133] the trial included women with both platinum-sensitive and -resistant disease. ORRs were appreciated in 33% of patients receiving the 400 mg twice daily dose and 13% of patients receiving the 100 mg twice daily dose. Further, women with platinum-sensitive and -resistant disease experienced ORRs of 38% and 30%, respectively, with the 400 mg dosing regimen. These encouraging results suggest that olaparib may be an efficacious and safe treatment option in BRCA-mutated advanced ovarian cancer.

Other PARP inhibitors, including veliparib, iniparib (BSI 201), and AG014699, are currently under investigation as monotherapy or in combination with other chemotherapeutic agents in women with recurrent ovarian cancer. Veliparib in combination with pegylated liposomal doxorubicin is being studied in a phase I trial of women with recurrent EOC, fallopian tube cancer, PPC, or metastatic breast cancer (NCT01145430). Iniparib in combination with carboplatin and gemcitabine is currently being studied in resistant ovarian cancer patients (NCT01033292). The results of these studies will certainly help to determine the role of PARP inhibitors in the treatment of recurrent ovarian cancers, including those with BRCA germline and somatic dysfunction.

Conclusion

Current available treatments for platinum-resistant ovarian cancer generally produce modest response rates approaching 20%, which indicates significant room for improvement. In addition to novel cytotoxic agents, emerging approaches based on small molecules and biologics now focus on targets critical to ovarian carcinogenesis, metastasis, and immune surveillance. A number of these targets have been examined in phase I and II clinical trials with encouraging results, and while early data are limited, further investigation with single-agent or combination therapies may offer new hope to women with this lethal disease.

Disclosure

The authors report no conflicts of interest.

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