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Updates on Anti-Cancer Therapy in Ovarian Cancer

Dana M Chase[1]*, Steven J Gibson[1], Bradley J Monk[1] and Krishnansu S Tewari[2]

[1]*The Division of Gynecologic Oncology, University of Arizona Cancer Center, Creighton University School of Medicine, St. Joseph's Hospital and Medical Center, Phoenix, USA*
[2]*The Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, The Chao Family Comprehensive Cancer Center, University of California, Irvine Medical Center, USA*

Abstract

Drug discovery in the ovarian cancer arena continues to launch important new clinical trials. Many biologic agents are being studied in phase II and phase III clinical trials for recurrent disease. These agents include compounds that disrupt angiogenesis through a variety of mechanisms. Other oncogenic pathways are also specifically targeted with investigational PARP, HDAC, MEK, topoisomerase and COX-2 inhibitors currently being studied. Various cytotoxic agents, as well as therapeutic vaccines, are also under investigation, and continue to demonstrate promising new data. The relevant agents in the treatment of ovarian cancer which have demonstrated positive phase II activity, will be discussed.

Keywords: Ovarian cancer; Chemotherapy; Targeted therapy; Angiogenesis; Recurrent cancer; Clinical trials

Introduction

Remissions after primary therapy in ovarian cancer is usually short-lived. Although intially responsive to a platinum and taxane-based therapy, recurrent disease is difficult to treat. Furthermore, there are few approved agents to treat recurrent ovarian cancer. Although patients that recur after 6 to 12 months of initial treatment may be retreated with a platinum plus taxane, those who relapse earlier or develop significant toxicity, may be given pegalated lipsomal doxorubicin, gemcitabine (in combination with platinum), etoposide, alkeran, topotecan, and/or hexamethylmelamide [1]. Unfortunately the response rate to these agents is generally less than 30%, and demonstrable survival benefits have not been shown. With the introduction of targeted drugs, such as trastuzumab in breast cancer, strategies in drug development have focused on the development of biologic agents that demonstrate selectivity for tumor tissue.

In 2010, we published on recent advances in drug discovery for ovarian cancer [1]. Since then, multiple drugs have either failed to advance into further development, or have newly been developed. For example, with respect to bevacizumab, several positive phase III trials have supported the use of this drug in upfront and recurrent ovarian cancer cases. In addition, trabectidin was previously discussed and also demonstrated positive phase III results, improving progression-free survival, and overall response rate in a 672 patient study [2]. Unfortunately, several of the drugs previously described have been found to be inactive, or with disappointing clinical outcomes. This review will thus highlight new drugs for ovarian cancer that have recently demonstrated positive phase II activity (Table 1). The ultimate goal with this drug development is to achieve prolonged remission and improved quality of life, for patients with recurrent ovarian cancer.

Targeted Agents

Angiogenesis inhibition

VEGF-dependent: Vascular endothelial growth factor (VEGF) is a signaling molecule involved in triggering the growth of blood vessels within cancers. The VEGF mechanism of action encompasses binding to tyrosine kinase transmembrane receptors (VEGFR), found on tumor endothelial cells, initiating angiogenesis (Figure 1) [3]. VEGFR-2 regulates cellular VEGF interactions, making it a crucial component in the angiogenic process. Modulating VEGF has become a highlighted area of study with potential in therapeutic interventions.

VEGF-Trap Antibody: Aflibercept: VEGF-Trap is a soluble fusion antibody consisting of portions of VEGFR-1 and VEGF-2, with high affinity for VEGF-A and VEGF-B, which is prevalent in human and several animal species. VEGF-Trap pharmacokinetics demonstrates a greater binding potential than monoclonal antibodies, as well as minimal interaction with the extracellular matrix [4]. *In vivo* studies utilizing a cell line that overexpresses VEGF, known as SKOV-3, reveal VEGF's contribution to the development of ascites, resulting from ovarian cancer. VEGF-Trap not only lowered ascites, but also drastically decreased the degree of tumor burden in mice that had been inoculated with OVCAR-3 cells [5]. The hypothesis is that VEGF-Trap inhibits leakage between endothelial cells within tumor vasculature, therefore, reducing the incidence of ascites [6].

Phase II trials of the VEGF-Trap agent aflibercept demonstrate its effectiveness in reducing malignant ascites. One randomized, placebo-controlled phase II study enrolled fifty-five women with advanced ovarian cancer and recurrent malignant ascites, and found women receiving aflibercept averaged thirty-one days, until repeat paracentesis, compared to eight days which in the placebo group. Fatal bowel perforations occurred in three patients receiving aflibercept, and only in one placebo group patient, demonstrating a notable clinical risk with VEGF-Trap in patients with advanced ovarian cancer [7]. Another phase II study also found benefit from aflibercept in the reduction of malignant ascites, with a 450% increase in the time to repeat paracentesis, when compared to the baseline interval. This study reports that the safety profile of aflibercept is consistent with that of

***Corresponding author:** Dana M Chase, The Division of Gynecologic Oncology, University of Arizona Cancer Center, Creighton University School of Medicine, St. Joseph's Hospital and Medical Center, Phoenix, USA, Tel: 602-406-7730; Fax: 602-798-0807; E-mail: Dana.chase@chw.edu

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Category			Agent/Patent (Manufacturer)	Mechanism
Targeted Agents	Angiogenesis Inhibition	VEGF-dependent	Aflibercept/US7635474 (Sanofi-Aventis)	Antibody binds to VEGF-A and VEGF-B (IV)
			Pazopanib/US7390799 (GSK)	Oral tyrosine kinase inhibitor binds to VEGFR, PDGFR, c-kit
			Ramucirumab/US6811779 (ImClone Systems)	VEGFR-2 human antagonist antibody (IV)
		VEGF-independent	AMG 386/US7618943 (Amgen)	Anti-ANG1/ANG2 antibody binds to PDGFR-α (IV)
			BIBF 1120/US7521425 (Boehringer Ingelheim)	Oral tyrosine kinase inhibitor binds to VEGFR, PDGFR, FGFR
			Lenalidomide/US7393862 (Celgene)	Oral thalidomide analog with immunomodulatory and anti-angiogenic properties
	PARP inhibitor		Olaparib/US6924284 (AstraZeneca)	Oral Poly (ADP-ribose) polymerase inhibitor
	Folic acid receptor antagonist		EC145/US7601332 (Endocyte)	Targets folate receptors (IV)
			Farletuzamab/US8124083 (Morphotek)	Humanized monoclonal antibody that targets folate receptor-α (IV)
	HDAC inhibitor		Belinostat/US7880020 (Topotarget)	Targets hydroxamic acid-type histone deacetylase enzymes (IV)
	MEK inhibitor		Selumetinib/US7425637 (AstraZeneca)	Oral MAPK kinase inhibitor
	Epothilone		Sagopilone/US7407975 (Bayer Schering Pharma)	Epothilone that binds to tubulin (IV)
	Topoisomerase inhibitor		Belotecan/US6265413 (Chong Kun Dang)	Inhibits Topoisomerase I (IV)
			Irinotecan/US7435726 (Pfizer)	Inhibits Topoisomerase I (IV)
			Etirinotecan pegol (NKTR102) /US7744861 (Nektar)	Inhibits Topoisomerase I (IV)
	COX-2 inhibitor		Celecoxib/US5972986 (Pfizer)	Oral inhibitor of cyclooxygenase-2 activity
	EGFR Inhibitor		Panitumumab/US7981605 (Amgen)	Oral humanized monoclonal antibody that binds specifically to external growth factor receptor
Immunotherapy			NY-ESO-1/US7632506 (Roswell Park Cancer Institute)	Vaccination that induces immune response to tumor
			Asparagine–glycine–arginine human tumor necrosis factor (NGR-hTNF)/US7795386 (MolMed)	Induces an antitumor immune response (IV)
			Catumaxomab/US8066989 (Trion Pharma)	Oral tri-functional antibody binds EpCAM, CD3, and Fc receptor
Cytotoxic agents			Polyglutamate paclitaxel/US7399860 (Cell Therapeutics)	Mitotic inhibitor (IV)
			Pemetrexed/US5217974 (Eli Lilly & Co.)	Thymidylate synthase inhibitor (IV)

Table 1: Updates in ovarian cancer drug discovery demonstrating positive phase II activity.

other anti-VEGF agents, with a grade 3 intestinal perforation occurring in one of the sixteen enrolled patients [8].

Anti-Ang1/Ang2 Antibody: AMG 386: Tyrosine kinase Tie receptors are bound by certain molecules (angiopoietins), involved in the production of vascular endothelial cells. One of these Tie receptor subtypes, Tie-2, has proven to be crucial in the activation of the angiogenesis cell signaling process. Prior studies have demonstrated that there is an interaction between VEGF and Angiopoietin 2 (Ang2), both of which are believed to contribute to the development of ovarian cancer [9,10]. One study using a murine ovarian cancer angiogenesis model found that VEGF resulted in Ang2 being expressed at significantly higher levels in tumor endothelial cells [9]. This same study hypothesized that VEGF creates a paracrine stimulation of angiogenesis during tumor proliferation, by inducing the Ang2 angiopoietin/Tie2 receptor. Other studies have implied that both Ang1 and Ang2 are involved in angiogenesis of ovarian tumor cells [10].

AMG 386 is an Ang1/Ang2 neutralizing antibody that interferes with the VEGF/Angiopoietin relationship, and is of interest in the treatment of ovarian cancer [11]. AMG 386 is a synthetic peptide that exhibits a high affinity for angiopoietins fused to the constant region of IgG1. A recent phase II, double-blind, placebo-controlled trial, combined AMG 386 with paclitaxel in patients with recurrent ovarian cancer. One hundred and sixty-one women were randomized to Arm A (10 mg/kg), Arm B (3 mg/kg), or Arm C (placebo). The study showed antitumor activity, with a correlation between the measured response and the AMG 386 dose, with progression-free survivals of 7.2 months, 5.7 months, and 4.6 months, respectively. The treatment was tolerable with a manageable safety profile, including peripheral edema, hypokalemia, and thromboembolic events, with no observed bowel perforations [12]. A similar phase II trial was conducted to explore the exposure-response relationship of open-label AMG 386, with weekly paclitaxel. Toxicity remained the same for both exposure groups. As reported in the previous AMG 386 with paclitaxel study, patients with high exposure to AMG 386, had a significantly longer progression-free survival (7.2 months) than those with low exposure (1.8 months) [13]. TRINOVA, a phase III trial sponsored by Amgen, is a nine-hundred patient study currently underway, whose results will be anxiously awaited [14].

VEGFR, PDGFR and c-Kit Tyrosine Kinase Inhibitor: Pazopanib: Pazopanib is a multi-targeted kinase inhibitor targeting VEGFR, PDGFR and c-Kit tyrosine kinases, and is currently being studied in an array of cancers [15]. Pazopanib has proven to considerably inhibit growth *in vitro* in tumor xenografts. Thirty-six ovarian cancer patients

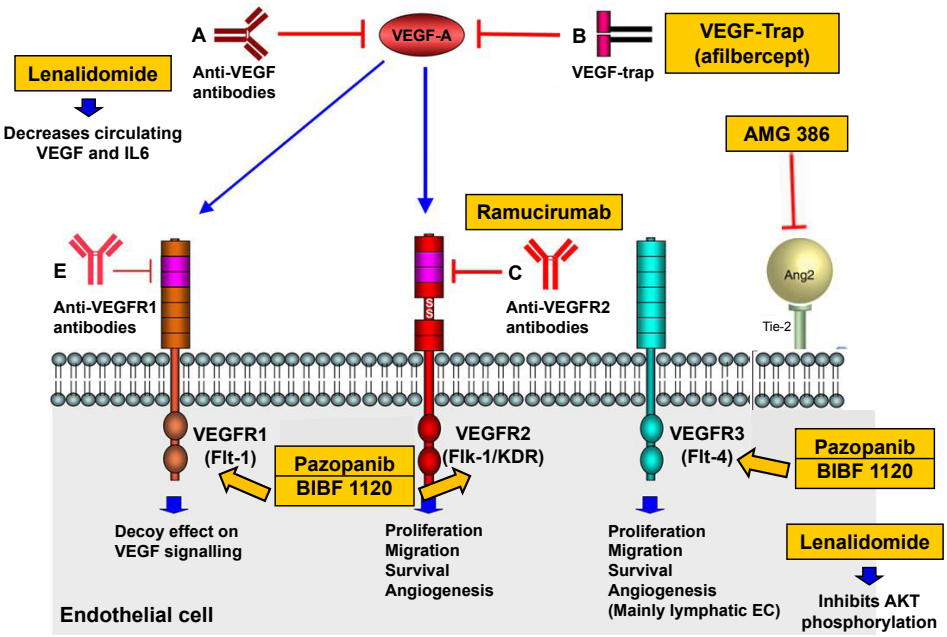

Figure 1: Agents Targeting the VEGF Pathway [1].

in an open-label, phase II study received 800 mg of oral pazopanib daily. Eleven (31%) of the patients had a CA-125 response to the treatment with toxicities, comparable to those of other small-molecule agents similar to pazopanib. The most common adverse events noted were grade three alanine and aspartate aminotransferase increases (each 8%). The median time to response was twenty-nine days, with an average response period of one-hundred and thirteen days [16]. The monotherapy was well tolerated and warranted a phase III trial, currently under investigation in the AGO-OVAR16 study, with approximately nine-hundred patients enrolled to evaluate the efficacy and safety of pazopanib monotherapy in ovarian cancer patients [17].

VEGFR-2 Antibody: Ramucirumab: Ramucirumab is a human monoclonal antibody targeted at the VEGFR-2 found on tumor endothelial cells, thus inhibiting the VEGF cascade, and potentially making it a useful anti-angiogenesis agent [18]. In a recent phase II study, sixty women with ovarian cancer were enrolled in an open-label study of ramucirumab monotherapy. The drug was administered every two weeks (8 mg/kg), and a median progression-free survival of 3.5 months and overall survival of 11.1 months were observed. Ramucirumab was reasonably tolerated, with no unexpected toxicities observed, demonstrating single-agent activity with approximately one-third (34.2%) of patients progression-free at six months [19].

VEGF-Independent

VEGF Receptor, Platelet-derived and Fibroblast Growth Factor Receptor: BIBF 1120: The additional targeting of proangiogenic receptors continues to be of interest, and has been proposed to improve the efficacy of VEGF blockade. BIBF 1120 is a molecule that simultaneously inhibits VEGF receptor, platelet-derived and fibroblast growth factor receptors [20]. When studied in animal tumor models, BIBF 1120 effectively reduced tumor blood vessel density and integrity [21].

This drug is administered orally in a twice daily continuous dosing schedule. A randomized, placebo-controlled phase II trial evaluated BIBF 1120 maintenance therapy (250 mg for 36 weeks), after chemotherapy in patients with relapsed ovarian cancer. Eighty-three women were enrolled and following the treatment cycle, the progression-free survival was 16.3% for BIBF 1120 patients and 5% for placebo patients. BIBF 1120 patients experienced a much higher rate of grade 3 or 4 hepatotoxicity (51.2%), compared to that of the placebo group (7.5%) [22]. The potential effect of BIBF 1120 nearly tripling progression-free survival, when compared to the placebo, has warranted a thirteen-hundred patient, phase III study of this drug in LUME-Ovar 1 [23].

Immunomodulatory Thalidomide Analog: Lenalidomide: Lenalidomide (Revlimid) is a thalidomide derivative, currently FDA-approved in the treatment of multiple myeloma. *In vitro*, Lenalidomide demonstrates an immunomodulatory role, and directly inhibits tumor development by disrupting the microenvironment support for tumor cells. *In vivo*, lenalidomide's anti-angiogenic and immunomodulatory properties contribute to tumor cell apoptosis [24].

A phase II GINECO study evaluated the efficacy of single-agent lenalidomide (20 mg daily), in women with asymptomatic late recurrent ovarian cancer. The study enrolled forty-five patients and produced promising results, demonstrating activity in the treatment of ovarian cancer. Non-progressive disease was measurable in 38% of patients at four months. Median progression-free survival data was 3.8 months; however, in the subset of patients with a platinum-free interval greater than twelve months, the progression-free survival observed was nearly doubled (6.4 months). The most common grade 3/4 toxicity was neutropenia, evident in 29% of women. The combination of a platinum-based chemotherapy with lenalidomide is currently under investigation [25].

Poly (ADP-ribose) Polymerase Inhibitor: Olaparib: Poly(ADP-ribose) polymerases (PARPs) are proteins involved in the repair of DNA [26]. PARPs assist in the repair of DNA single-strand breaks, by repairing base excisions. BRCA1 and BRCA2 proteins involved in DNA recombination play crucial roles in repairing double-strand breaks, and can do so in the setting of PARP inhibition. However,

PARP inhibition in BRCA-deficient cells results in the incapability to repair DNA damage induced by chemotherapy. In a BRCA-deficient environment, cell death can manifest when DNA breakage is not repaired, and the cell is exposed to such agents as PARP inhibitors, that hinder single-strand break repair.

BRCA mutations represent a minority of breast and ovarian cancers. These homozygous mutations, that are unique to the tumor cells, result in the inability to repair DNA which then can be exclusively targeted by a PARP inhibitor, preserving the patient's non-tumor cells. Preclinical studies discussed by Fong et al. [27] demonstrate that BRCA-deficient cells were 1000-fold more sensitive to PARP inhibitors. A randomized phase II study enrolled one-hundred and fifty-six women to compare oral olaparib (200 mg) with paclitaxel and carboplatin, followed by olaparib maintenance monotherapy (400 mg) (Arm A) versus paclitaxel and carboplatin alone (Arm B). The addition of olaparib in Arm A showed a significant improvement in progression-free survival (12.2 months *vs.* 9.6 months, respectively), while the objective response rate remained pretty similar (64% *vs.* 58%). The most common adverse events during the combination phase were alopecia, nausea and fatigue. Overall survival data is pending; however, with improvement in progression-free survival, improved overall survival data would warrant further investigation in phase III studies [28].

Folate Receptor Antibody: EC145: Folate receptors are highly expressed in cancer cells, since folic acid is a crucial component in rapid cell division, so an interest has been placed on targeting these cancer cells with highly expressed folate receptors with chemotherapy (Figure 2). EC145 is a drug comprised of a folate and vinca alkaloid combination that is used to target the folate receptors. Folate receptors are over-expressed in numerous types of human tumors, including cancers of the ovary, lung and kidney [29]. Historically vinca alkaloids have constituted drugs that bind to tublin, to inhibit cell replication and division, such as vincristine or vinblastine. The combination of vinca alkaloids with folate is thought to reduce toxicity by specifically targeting cancer cells. EC145 also specifically contains desacetylvinblastine monohydrazide (DAVLBH), which has a related mechanism to the other vinca alkaloids.

In preclinical studies, EC145 had a high affinity for FR-positive cells, and showed activity in both *in vitro* and *in vivo* models in FR-positive tumors [30,31]. Since folate receptors are highly expressed in ovarian and endometrial cancer, EC145 was studied and well-tolerated in 16 patients with these cancer types. EC145 was combined with pegylated liposomal doxorubicin (PLD), and evaluated in a phase II clinical trial, for the treatment of advanced ovarian and endometrial cancers. Patients underwent a FolateScan during the screening period, to confirm eligibility for the trial. This scan uses a technetium-based imaging agent (EC20), which can be utilized to identify patients whose tumors express FR, and will most likely benefit from EC145 treatment. Patients were randomized, and either received EC145 (2.5 mg, 3 times a week on weeks 1 and 3) plus PLD (50 mg/m^2 every 28 days), or PLD alone. This study was a first in finding a significant improvement in progression-free survival, with EC145 treatment in women with platinum-resistant ovarian cancer [32]. A six-hundred and forty patient, phase III clinical trial is currently underway for further evaluation of EC145, combined with PLD, in this patient population [33].

Hydroxamic Acid-type Histone Deacetylase Inhibitor: Belinostat: Belinostat is a histone deacetylase inhibitor that has been well tolerated in the preclinical setting, and effective in combination with chemotherapy in the treatment of ovarian cancer. Belinostat works to normalize the mutated gene patterns expressed in cancer cells. Data shows that belinostat is a key player in tumor cell apoptosis, and the inhibition of cell proliferation. Belinostat is in multiple late-stage trials with over one-thousand patients, already treated with the study drug [34].

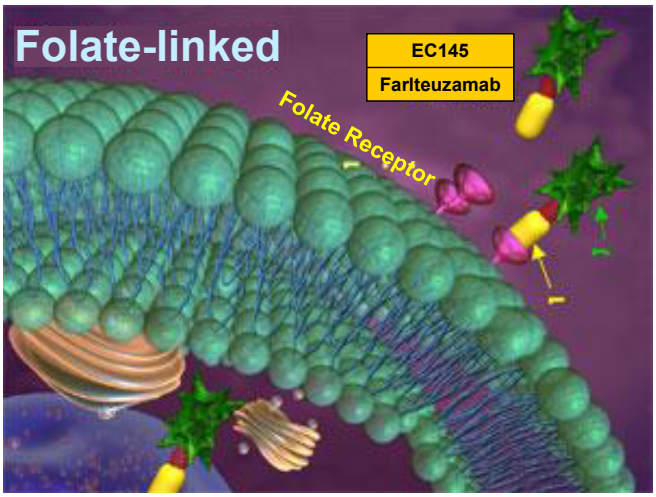

Figure 2: Folic Acid Receptor Antagonists [70].

A phase II trial evaluated belinostat (1000 mg/m^2 daily for 5 days), combined with carboplatin and paclitaxel, in patients with recurrent ovarian cancer. Thirty-five women were enrolled, and the primary endpoint of the study was overall response rate. Fifteen patients (43%) responded to the treatment (three partial and twelve complete responses); however, platinum-sensitive patients had a significantly better overall response (63%), compared to the resistant group (44%). The most common toxicities observed in over half of the patients were nausea, fatigue, vomiting and alopecia. Forty-eight percent of patients were progression-free at six months. Belinostat shows promise in heavily pretreated ovarian cancer patients, when combined with this platinum-based therapy [35].

MAPK Kinase Inhibitor: Selumetinib: Selumetinib is a mitogen-activated protein kinase inhibitor that shows preclinical benefit in targeting the MEK oncogenic pathway. The small molecular agent is a protein regulator in activated oncogenic pathways expressed in ovarian cancer patients. Results from a phase II study indicate positive activity in the treatment of ovarian cancer. Fifty-two women received two 100 mg doses of selumetinib daily in the clinical trial, and grade four adverse events were only observed in three patients (6%). Thirty-four (63%) of the women in the study had a progression-free survival of more than six months, with a median overall survival of eleven months [36].

Epothilone: Sagopilone: Sagopilone is the first fully synthetic epothilone that has shown promising activity in tumor xenografts models of human breast, prostate, cervical, ovarian, and many other types of cancers. One phase II trial evaluated sagopilone single agent activity in a randomized, open-label study. The study enrolled sixty-three women and administered sagopilone (16 mg/m^2), at two different infusion schedules (3-h or 0.5-h every 21 days for 6 weeks). The 0.5-h infusion arm was terminated due to a failure to meet efficacy requirements. Nine tumor responses were observed in the 3-h arm (14%), and the most common toxicites were peripheral sensory neuropathy (73%), nausea (37%) and fatigue (35%). This study showed

sagopilone efficacy and tolerability in patients with platinum-resistant ovarian cancer [37]. Another phase II study combined sagopilone with carboplatin in women with recurrent platinum-sensitive ovarian cancer. Forty-five women were enrolled and received the same infusion schedule, as the previous study (3-h, 16 mg/m^2 every three weeks), followed by carboplatin. Twenty-nine tumor responses were observed (64%), with the same expected adverse events. With manageable toxicities and efficacy in both platinum-resistant and platinum-sensitive ovarian cancer patients, phase III trials of sagopilone are anticipated [38].

Topoisomerase I Inhibitor: Belotecan: Belotecan is a camptothecin derivative that works by inhibiting topoisomerase I, and has shown antitumor characteristics in preclinical data. One phase II study evaluated the activity of daily belotecan (0.5 mg/m^2), as a single agent in the treatment of refractory or recurrent ovarian cancer. Sixty-three women received the drug for five days every three weeks, and there was a reported overall response of 30.2%, with nine of the patients having complete remission. Platinum-sensitive patients had a better response, when compared to platinum-resistant patients. The median progression-free survival for both groups was 6.5 months, and toxicities were manageable [39]. Because belotecan demonstrated single agent activity and efficacy in ovarian cancer, phase II combination trials with carboplatin have been investigated. Thirty-eight women received belotecan (0.3 mg/m^2) for five days and carboplatin on the fifth day, every three weeks. The overall response rate was 57.1%, with a median progression-free survival of seven months. Toxicites included neutropenia (28.8%), thrombocytopenia (19.8%) and anemia (14.4%). The addition of carboplatin to belotecan nearly doubled the response rate, while toxicities remained similar [40].

Irinotecan: Irinotecan is a topoisomerase I inhibitor that works by preventing DNA from unwinding, and therefore, impedes tumor cells from replicating (Figure 3). Irinotecan was first FDA-approved in 1996, and has been approved for the treatment of metastatic colorectal cancer [41]. Given the effectiveness of irinotecan in other cancers, the agent was recently studied, in combination with the anti-angiogenesis agent, bevacizumab, in women with pretreated recurrent ovarian cancer. The phase II trial enrolled twenty patients, and administered irinotecan (250 mg/m^2) and bevacizumab (15 mg/kg), every three weeks. Partial response was observed in three patients with stable disease, present in nine of the fifteen women measureable at that time. The most common toxicities were grade three diarrhea and neutropenia. The median progression-free survival was 9.6 months, and when measured at six months, 61% of patients were progression-free. The overall survival in the study was 15.5 months, and thus, encouraging given the heavily-pretreated status of the patients [42].

Etirinotecan pegol: Etirinotecan pegol is a next-generation topoisomerase I inhibitors. When normal topoisomerase I inhibitors like irinotecan and belotecan are quickly dispersed within the body, they not only damage healthy tissues, but also have poor half-lives, and do not sufficiently expose the tumor to the concentrated therapeutic agent. Etirinotecan pegol, instead connects small cytotoxic agents to a macromolecular polymer, using specialized linkers. These linkers are then slowly metabolized, resulting in a continuous, controlled release of the chemotherapy, which works as previously described by inhibiting topoisomerase I, and thus, hindering the division of the tumor cells. Preclinical studies have shown a 300-fold increase in the chemotherapy concentration, within the tumor, when compared to other topoisomerase I inhibitors. Along with this, increased effectiveness in tumor concentrations, the half-life of this agent has improved to fifty days, with activity in circulation throughout the entire cell cycle [43].

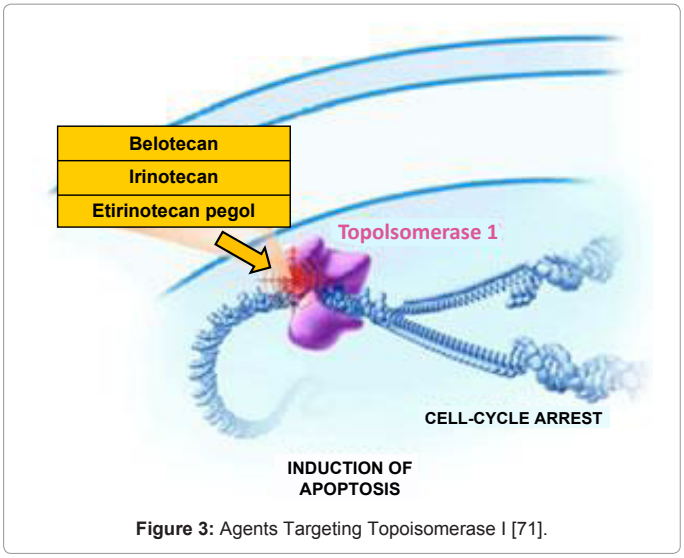

Figure 3: Agents Targeting Topoisomerase I [71].

Clinical trials are under investigation for the use of this agent in various cancers, including ovarian cancer. A phase II open-label study evaluated etirinotecan pegol (145 mg/m^2), every 14 or 21 days in seventy-one women, with resistant or refractory ovarian cancer. Patients who received the agent every fourteen days had a higher response rate (47%), than those who received it every twenty-one days (41%). Respective CA-125 responses were 61% and 52%, and usually occurred within one month of drug administration. The most common toxicities included diarrhea, dehydration, hypokalemia and fatigue. Planning for a phase III investigation is currently underway [44].

Cyclooxygenase-2 Inhibitor: Celecoxib: Celecoxib is an anti-inflammatory agent that works through the inhibition of the Cyclooxygenase-2 (COX-2) enzyme [45]. New studies have found that over-expression of the COX-2 enzyme often leads to ovarian cancer patients being resistant to platinum-based chemotherapy, so recent clinical trials have examined the combination of celecoxib, with current chemotherapy treatments [46]. One prior phase II trial combined celecoxib with docetaxel plus carboplatin in two-hundred and one women with advanced ovarian cancer, and found that the addition of celecoxib had no effect on progression-free survival, overall survival, or CA-125 response [47]. However, a more recent phase II study combined celecoxib with carboplatin, and found it to be a well tolerated treatment with encouraging results, in women with heavily pre-treated recurrent ovarian cancer. Forty-five women were enrolled and 28.9% responded to the treatment. The most common toxicities observed were neutropenia, anemia, and thrombocytopenia [46].

Cytotoxic Agents

Mitotic inhibitor

Polyglutamate paclitaxel: Polyglutamate paclitaxel is an agent that utilizes polyglutamate drug delivery technology, similar to that described in etirinotecan pegol above. These polyglutamate molecules are much larger than standard paclitaxel molecules, allowing them to lodge themselves into tumor tissue, through leaky tumor vasculature. The drug remains inactive in the bloodstream, and is too large to fit through normal vasculature, so it specifically targets only tumor cells. Once inside the tumor tissue, the agent is slowly metabolized by the

tumor cells, resulting in the controlled release of the cytotoxic agent. This process reduces toxicity to healthy tissues, while increasing efficacy [48]. Polyglutamate paclitaxel falls into the mitotic inhibitor drug class, and is under investigation in the treatment of ovarian cancer [49].

Polyglutamate paclitaxel, brand name OPAXIO, is under development, and is currently completing an eleven-hundred patient randomized phase III trial, comparing twelve cycles of maintenance therapy OPAXIO to twelve cycles of maintenance therapy paclitaxel versus no treatment [50]. Previous phase II results that encouraged this phase III trial evaluated carboplatin with OPAXIO in eighty-two women with advanced ovarian cancer. The study reported 98% of patients having a CA-125 tumor response, with complete response occurring in 85% of patients and partial response in 12%. The most common grade 3/4 adverse events were neutropenia (92%), thrombocytopenia (55%) and neuropathy (23%) [51].

Thymidylate synthase inhibitor

Pemetrexed: Pemetrexed is a targeted cytotoxic agent that inhibits thymidylate synthase and other folate-dependent enzymes within a cell that are necessary for perforation [52]. Pemetrexed disodium was FDA-approved in July of 2009, for the treatment of non-squamous non-small cell lung cancer, and is currently being studied in clinical trials for ovarian cancer [53]. The addition of pemetrexed to the anti-angiogenesis agent bevacizumab was explored in a recent phase II clinical trial. Thirty-four women with recurrent or persistent ovarian cancer were given pemetrexed (500 mg/m^2), and bevacizumab (15 mg/kg), every three weeks. The twelve-month overall survival data was 88%, with a median progression-free survival of 7.8 months. Hematologic toxicities occurred in 53% of patients, as well as observed metabolic (29%), constitutional (18%), pain (18%), and gastrointestinal (15%) adverse events. This tolerable and highly active combination treatment warrants further evaluation in phase III studies [54].

Therapeutic Vaccines

Anti-tumor immune response vaccine

NY-ESO-1: The antigen NY-ESO-1 is a germ cell protein specific to the testes and various cancers, and is distinctively expressed by cancer cells [55]. The expression of NY-ESO-1 is notably high in ovarian cancer [56]. Its gene has been mapped to chromosome Xq28, and it is just one of many cancer-testes antigens. The antigen is found at increased levels in advanced stage cancers and antibodies, and cellular immune responses have been documented in tumors that express this antigen [56]. In ovarian cancer patients, NY-ESO-1 is being used as a vaccine to prompt an immune response against advanced stage patients.

In a phase II study, the efficacy of NY-ESO-1 in ovarian cancer patients was reported. Twenty-two women with advanced epithelial ovarian cancer received recombinant vaccinia-NY-ESO-1, followed by booster fowlpox-NY-ESO-1. The median progression-free survival was twenty-one months, with a median overall survival of forty-eight months. This preliminary data shows clinical benefit from the treatment, and justifies further investigation with this antigen [57].

Anti-tumor immune response vaccine

NGR-hTNF: Asparagine–glycine–arginine human tumor necrosis factor (NGR-hTNF) is a fused agent, comprised of CNGRC and hTNF peptides. The CNGRC peptide specifically targets an isoform of the CD13 receptor and binds to it, planting itself in the tumor vasculature, without interfering with the CD13 receptors of healthy cells. The hTNF is then exposed to the tumor site, allowing NGR-hTNF to increase vascular permeability of the tumor vessels. The NGR-hTNF effect on tumor vasculature has sparked interest in various combination trials, with chemotherapeutic agents that would allow the cytotoxic agents to be more effective in tumor tissues, and less toxic in healthy tissues [58].

One phase II combination study of NGR-hTNF with doxorubicin enrolled thirty-seven women with relapsed ovarian cancer. Patients received NGR-hTNF (0.8 μg/m^2) and doxorubicin (60 mg/m^2) on day 1, every three weeks. The median progression-free survival in the study population was five months, with an overall survival of seventeen months. The only noted adverse events were grade 1/2 chills (65%), and the overall disease control rate reported was 66% [59]. The results of a separate, randomized phase II trial by MolMed are anticipated [60].

EpCAM, CD3, and Fc receptor antibody

Catumaxomab: Catumaxomab is classified as a tri-functional antibody, with a structure comprised of an anti-EpCAM antibody and an anti-CD3 antibody. This allows catumaxomab to bind to the antigen EpCAM on tumor cells, the CD3 molecules on T cells, and to the Fc receptor on accessory cells, and by doing so, it triggers an antitumor immune response [61].

An open-label, phase II study of catumaxomab in patients with malignant ascites enrolled thirty-two women, and found almost one-fourth (22.6%) of patients had at least a 400% increase in their platinum-free interval after catumaxomab treatment. Patients received catumaxomab (10, 20, 50, 150 μg) on days 0, 3, 7, and 10. The median overall survival was 3.6 months, and the toxicities were tolerable and consistent with what would be expected for this type of antibody [62]. Another single-arm phase II study administered one intraoperative (10 μg) and four postoperative (10, 20, 50, 150 μg) doses of catumaxomab on days 7, 10, 13, and 16. The study found a 3-year survival benefit in patients who received catumaxomab, when compared to a match-pair control group, with the respective survival rates being 85.4% and 63.4% [63]. The favorable survival data initiated a phase III trial in two-hundred and fifty-eight EpCAM-positive cancer patients with malignant ascites [64].

Humanized monoclonal antibody

Panitumumab: Panitumumab is another humanized monoclonal antibody. Brand named Vectibix, panitumumab was FDA-approved in September 2006, in the treatment of EGFR-expressing colorectal cancer [65]. The agent works by specifically binding to the external growth factor receptor, and therefore, inhibiting the activation of this oncogenic pathway which is overexpressed in many cancer types. Preclinical data suggest that panitumumab causes cell cycle arrest, as well as having some anti–angiogenic properties [66]. Panitumumab is being studied in cancers that overexpress the EGFR oncogene, such as ovarian cancer.

Forty-six platinum-resistant ovarian cancer patients with KRAS wild-type were enrolled in a multicenter phase II study of panitumumab (6 mg/kg days 1 and 15), with pegylated liposomal doxorubicin (40 mg/m^2 day 1), every four weeks. With eight women having a CA-125 response, the overall response rate was 24.3%. The reported progression-free survival was 2.7 months with an overall survival of 8.1 months. Observed toxicities included skin toxicity (42%), fatigue (19%) and vomiting (12%). This combination trial demonstrated efficacy in the studied population, for the treatment of platinum-resistant ovarian cancer [67]. One current phase II trial is recruiting patients to evaluate

the combination of panitumumab with gemcitabine, while another study is evaluating carboplatin-based chemotherapy with panitumuab in relapsed ovarian cancer patients [68,69].

Current and Future Developments

As the inclusion of unconventional agents are increasingly incorporated into clinical trials and practice, the hope is that drug discovery will be encouraged in all areas of cancer therapy, from improving our ability to predict response to chemotherapy, to enhancing the delivery of drugs to targeted tissues. As stated previously in an earlier review [1], with the future of cancer treatment moving towards a morepersonalized approach, the goal is that an individual profile will be determined, and thus agents used that target key pathways in this individual's cancer.

Conflict of Interest

Dr. Tewari reports that he does have contracted research with Biogen Idec, Amgen, Genentech, US Biotest, and Precision Therapeutics.

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