Original Article

Novel Non-Cytotoxic Therapy in Ovarian Cancer: Current Status and Future Prospects

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Key Words

Ovarian cancer/carcinoma, novel therapy, non-cytotoxic therapy, targeted therapy, molecular targets

Abstract

Although significant improvements in standard therapy for ovarian carcinoma have been made over the past decade, current treatment is limited by the development of resistance to cytotoxic chemotherapy, and most women ultimately die of the disease. New knowledge of the biology of ovarian cancer has led to the identification of potential molecular targets that are differentially expressed in normal cells versus cancer cells, and advances in pharmacology have led to the development of novel agents that work differently from traditional cytotoxic chemotherapy by exploiting these targets. Many of these agents are being evaluated in clinical trials. This article discusses molecular targets that are important in ovarian carcinoma, including angiogenesis, tyrosine kinases, mitogen-activated protein kinases, and phosphatidylinositol-like kinases such as mammalian target of rapamycin, and the proteosome. This article reviews novel non-cytotoxic agents that target these pathways and are currently being evaluated in ovarian carcinoma treatment. (*JNCCN* 2006;4:955–966)

Ovarian cancer is the eighth most common cancer and the fifth leading cause of cancer mortality in women in the United States. An estimated 20,180 new cases and 15,310 deaths will occur from ovarian cancer in 2006.[1] The current standard of care is aggressive surgical cytoreduction followed by chemotherapy typically consisting of a platinum agent and a taxane. Although 5-year survival has improved,[1] most women with ovarian cancer ultimately die of the disease. Improvement in survival over the past decade is attributed mainly to the discovery and integration of more active cytotoxic therapy in the front-line setting and at recurrence. Unfortunately, current treatment of ovarian cancer is limited by patients developing resistance to cytotoxic chemotherapy. Recent emphasis has been on evaluating novel agents that work differently from traditional cytotoxic chemotherapy and therefore may benefit patients in the setting of resistant disease, either alone or through enhancing the activity of currently available cytotoxic treatments.

Although malignant cells use many of the same signaling pathways as normal cells, exploitable differences may exist that can be targeted with molecular therapeutics. Significant redundancy and plasticity of signaling and other biochemical pathways occur in cells. Ultimately, cancer seems to arise because these normal pathways are disrupted. Sometimes malignant cells acquire mutations that cause their growth to become dependent on a particular pathway or process, or for which a particular pathway confers a growth advantage. For example, hundreds of tyrosine kinases[2] mediate many normal cellular processes and signaling pathways. Mutations of various tyrosine kinases have been implicated in malignant transformation and tumor progression,[3,4] making them attractive therapeutic targets in cancer treatment. For example, the epidermal growth factor receptor (EGFR) is up-regulated in many solid cancers, and multiple approaches to target this receptor have been successful in cancer treatment.[5,6]

More knowledge about the biology of carcinogenesis and potential targets for therapeutics has coincided with advances in pharmacology. This was initially seen in hematologic malignancies, which may result from a single mutation, such as in the case of chronic myelogenous leukemia (CML) and the Philadelphia chromosome, which is present in most patients with CML and causes

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activation of the proto-oncogene BCR-ABL.[7] Imatinib mesylate is a potent inhibitor of the tyrosine kinase activity of BCR-ABL and has shown great efficacy in this disease.[8]

The area of solid tumors seems more complex, because molecular heterogeneity occurs within solid tumors and the microenvironment of the tumor or the malignant cell may play a role in its growth and survival. For example, tumors require new blood vessels to form to deliver blood and nutrients for continued growth and progression. Antiangiogenic agents target the signaling pathways of endothelial cells in tumors, and thus affect tumor viability by influencing angiogenesis.

Because a high degree of redundancy exists in signaling pathways in the cell and many tyrosine kinases have similar activating pathways, inhibitors developed against a particular tyrosine kinase may inhibit multiple tyrosine kinases. Imatinib, for example, inhibits the BCR-ABL tyrosine kinase activity, but also inhibits the platelet-derived growth factor receptor (PDGFR) and c-kit. This has led to its investigation and approval for treating gastrointestinal stromal tumors, which overexpress and often carry gain-of-function mutated c-kit.[9]

This article discusses novel treatment approaches for ovarian carcinoma (Table 1). Many agents have not been tested in large numbers of patients with ovarian carcinoma, but have shown promise in treating other malignancies. In those cases, this article briefly explains the specific pathway and the reasons it is a potential target for treating ovarian carcinoma. The article

Table 1 Novel Therapy Under Study for Ovarian Cancer

Agent	Mechanism of Action	Phase of Testing in OEC	Synergy with Chemotherapy
AMG 706	Receptor tyrosine kinase inhibitor targeting all known VEGF receptors, PDGFR, c-kit and c-Ret	I – II	Suspected
Bevacizumab	Monoclonal ab binds VEGF	III	Yes
BMS-214662	Farnesyl transferase inhibitor	I	Suspected
Bortezomib	Proteosome inhibitor	I	Suspected
Cetuximab	Monoclonal antibody that binds EGFR	I	Yes
Erlotinib	Reversible, selective inhibitor of EGFR	II single-agent I - II with chemotherapy	Suspected
Everolimus	mTOR inhibitor	I	Unknown
Flavopiridol	Depletes cyclin D1, binds to dsDNA, inhibits cyclin dependent kinase	I	Suspected
Lapatinib	Reversible inhibitor of Erb 1 and Erb 2	I – II	Yes
Lonafarnib	Farnesyl transferase inhibitor	III	Suspected
Ovarex	Monoclonal antibody to CA-125	III	Unknown
Pertuzumab	Monoclonal antibody binds to extracellular domain of HER-2	II	Suspected
PTK 787	Receptor tyrosine kinase inhibitor targeting VEGFR-1/Flt-1, VEGFR-2/KDR, VEGFR-3/Flt-4, PDGFR, KIT	I	Suspected
Sorafenib	Competitive inhibitor of ATP binding to Raf	II	Suspected
SU11248	Receptor tyrosine kinase inhibitor targeting PDGFR, VEGFR, KIT, FLT3	I	Unknown
TLK286	Glutathione-S transferase analogue targeting Glutathione-S transferase P1-1	II	Yes
Trastuzumab	Monoclonal antibody binds to extracellular domain of HER-2	II	Yes
VEGF Trap	Recombinant fusion protein binds VEGF A, VEGF B, PlGF1, PlGF2	II	Unknown

focuses on the pathways that appear to be most important in ovarian carcinoma and on agents that currently appear most promising. For a complete listing of all agents currently under evaluation for the treating ovarian cancer, please visit the Clinical Trial Web site (http://www.clinicaltrials.gov).

Antiangiogenesis

Access to oxygen and nutrients is vital to tumor growth. One way that tumors seem to obtain these vital substances is by creating new blood vessels, a process known as *angiogenesis* (Figure 1). Angiogenesis also appears to play a role in tumor metastasis by providing access to the systemic lymphatic and circulatory systems. Inhibiting angiogenesis is an appealing approach to controlling malignant disease. One hypothetical concern is that impairing the vascular supply to tumors might lead to tumor hypoxia and resistance to cytotoxic agents and radiotherapy. However, clinical trials show synergy with antiangiogenic treatment and traditional cytotoxic therapy and radiotherapy.[10–12] Experts have suggested that new blood vessels in tumors are aberrant and, therefore, are unable to efficiently deliver oxygen and chemotherapeutics to tumors. They suggest that antiangiogenic agents actually stabilize these new blood vessels, thereby improving delivery of oxygen, nutrients, and cytotoxic agents. The improved nutrient and oxygen supply ensures that proportionally more of the tumor cells are undergoing rapid growth, thereby making them more susceptible to radiotherapy and systemic cytotoxics, which attack cells during their growth phase.[13,14]

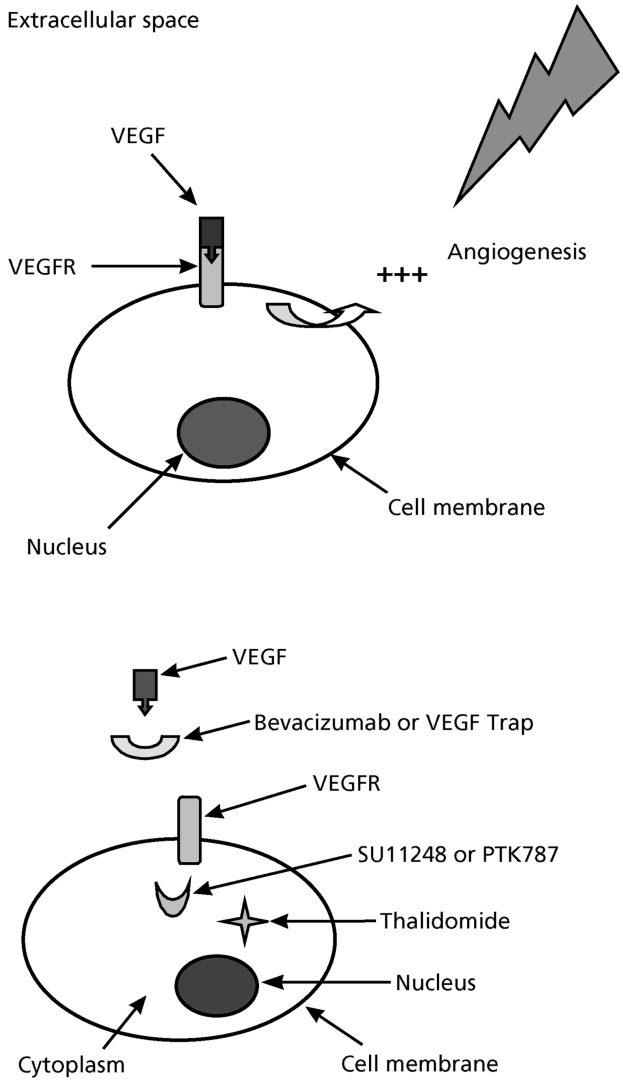

Figure 1 The upper diagram illustrates normal angiogenesis, which is stimulated by binding of VEGF to the VEGFR; the lower diagram illustrates the angiogenesis inhibitors and how they interfere with angiogenesis either in the extracellular space or in the cytoplasm.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF).[15] VEGF is overexpressed in many human cancers, including ovarian cancer.[16–18] Overexpression of VEGF seems to predict a poor prognosis in patients with ovarian cancer.[19,20] Interestingly, it appears to be present at high levels in ascitic fluid in patients with ovarian cancer complicated by ascites.[21]

The early trials with this agent did not include patients with ovarian carcinoma, and the first report of using bevacizumab in ovarian cancer was published in 2005.[22] In this case report, the patient had primary refractory disease and had progressed through multiple regimens before receiving bevacizumab, which produced a partial response and an improved performance status. Subsequently, the Gynecologic Oncology Group (GOG) conducted a phase II trial evaluating bevacizumab as a single agent in the second- or third-line setting, showing notable results. These included a 17.7% objective response rate, a 38.7% 6-month progression-free survival (PFS) rate, and a median PFS of 4.8 months.[23] Early results of a phase II trial of bevacizumab combined with low-dose metronomic oral cyclophosphamide also had a notable partial response rate of 28% and a disease stabilization rate of 59%, with a median PFS of 5.8 months among the 29 patients evaluable when the results were presented.[24] This trial is currently in the second stage of accrual. Bevacizumab

is also being evaluated in the front-line setting in combination with standard chemotherapy.

GOG 218 is an ongoing phase III, 3-arm, randomized, double-blind, placebo-controlled trial comparing carboplatin and paclitaxel with or without bevacizumab. In this trial, all patients receive 6 cycles of carboplatin and paclitaxel every 21 days, with either placebo or bevacizumab given with chemotherapy starting with the second cycle. The patients in arm 1 receive placebo with chemotherapy and then every 21 days after chemotherapy is completed for up to 22 cycles. Patients in arm 2 receive bevacizumab with chemotherapy and then receive placebo every 21 days for up to 22 cycles. Those in arm 3 receive bevacizumab with chemotherapy and then every 21 days after chemotherapy for up to 22 cycles.

Bevacizumab is also being evaluated in combination with erlotinib (see later section) for treating ovarian cancer in women whose disease is refractory to platinum and taxane. Experts have suggested that combining bevacizumab, an antiangiogenesis drug, and erlotinib, an EGFR receptor inhibitor, may inhibit multiple signal transduction pathways and reverse cancer progression in this difficult-to-treat population. Previous studies of this combination in non-small cell lung cancer, renal cell carcinoma, and metastatic breast cancer have indicated a potential synergistic effect for these two agents.[25–27]

VEGF Trap

AVE0005 (VEGF Trap) is a recombinant fusion protein composed of a portion of the extracellular domains of the VEGF receptor fused to the Fc portion of human IgG1.[28] It binds to VEGF A, VEGF B, and placental growth factors 1 and 2 (PlGF1 and PlGF2). In a phase I trial of this agent in patients with solid tumors, 1 patient with ovarian cancer experienced a partial response and improved performance status. These results led to a phase II trial evaluating VEGF Trap as a single agent in ovarian cancer, which is currently accruing patients. Preclinical data from a human ovarian cancer model suggest synergy with paclitaxel.[29]

Thalidomide

Thalidomide was initially used to treat morning sickness and was withdrawn because of teratogenicity, which was believed to be caused by inhibition of blood vessel development in the fetus.[30] Thalidomide appears to have immunomodulatory effects in addition to its antiangiogenic effects. It can either up- or down-regulate tumor necrosis factor-α (TNF-α), partially by interacting with nuclear factor kappa B (NF-κB). It appears to suppress interleukin-12 (IL-12) production and may augment T-cell activity.[31]

Although it has shown significant activity in multiple myeloma,[32–34] thalidomide has limited experience in treating ovarian cancer. A trial in Britain studying the effects of low-dose thalidomide in melanoma, renal cell carcinoma, ovarian cancer, and breast cancer found that only 1 of 19 patients with ovarian cancer experienced disease stabilization, and none experienced a response to treatment.[35] In a pilot study in the United States that enrolled 10 patients, 2 quit before completing 1 month of treatment; 2 of the remaining 8 experienced significant declines in CA 125; and 1 experienced a measurable response based on Response Evaluation Criteria in Solid Tumors criteria.[36] In the phase II setting, treatment with thalidomide combined with topotecan was compared with topotecan alone, and preliminary results were recently presented.[37] A current GOG trial is evaluating this agent in patients with rising CA 125 values and no measurable disease.

SU11248 (Sunitinib)

SU11248 is an oral, multitargeted, receptor tyrosine kinase inhibitor targeting PDGFR, vascular endothelial growth factor receptor (VEGFR), KIT, and FLT3. In a phase I trial of this agent in patients with advanced solid tumors, 2 patients had ovarian cancer, with 1 remaining on this agent for more than 20 weeks.[38]

PTK 787 (ZK 222584, Vatalanib)

PTK787 is an oral angiogenesis inhibitor that targets multiple VEGFR tyrosine kinases, including VEGFR-1/Flt-1, VEGFR-2/KDR, VEGFR-3/Flt-4, the PDGFR tyrosine kinase, and the c-kit protein tyrosine kinase.[39] Therefore, it is being evaluated in cancers that overexpress these receptors, including ovarian cancer. Preliminary results from a phase I study evaluating this agent combined with paclitaxel and carboplatin in the front-line treatment of patients with advanced disease showed that the combination was well tolerated and feasible.[40] It is currently being evaluated in the setting of recurrent disease in combination with docetaxel.

AMG 706

AMG 706 is an oral multikinase inhibitor targeting all known VEGFRs, PDGFR, c-kit, and c-Ret. In a phase I clinical trial in patients with advanced solid tumors, AMG 706 was well tolerated and had a broad

range of activity.[41] It is currently being evaluated in multiple phase I trials in combination with agents that have known activity in ovarian cancer, including paclitaxel, docetaxel, and carboplatin, and the GOG will soon conduct a phase II trial assessing AMG 706 as a single agent in recurrent ovarian cancer.

AZD2171

AZD2171 is an oral VEGFR-2 inhibitor that has shown efficacy in the preclinical setting[42] and is being evaluated as a single agent in recurrent disease in the phase II setting. The International Collaborative Ovarian Neoplasm Group is evaluating this agent in combination with platinum-based therapy in recurrent, platinum-sensitive disease.

Inhibition of the erb Family of Tyrosine Kinases

The erb family of tyrosine kinases is composed of 4 transmembrane receptors: EGFR or HER1/ErbB1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4.[43] Each receptor has a unique pattern of ligand binding and activation, generally through dimerization with each other to form homodimers or heterodimers.[44] The erb family of receptors has been shown to be important in directing growth and differentiation of epithelial cells during fetal development, and in malignant transformation and disease progression in many epithelial cancers.[45,46] Although evidence conflicts regarding the importance of these receptors' expression and their prognosis in ovarian cancer,[47–51] they are nonetheless an attractive target for further research in treating this disease.

Two main strategies for targeting these membrane receptors were developed. Monoclonal antibodies are large molecules that bind to an epitope on the receptor at its extracellular domain, inhibiting binding of the activator ligand or dimerization (Figure 2). They are typically administered intravenously and have long half-lives. Small molecules cross the cell membrane and bind to the intracellular portion of the receptor, blocking activity of the kinase. These are typically administered orally and have a short half-life, requiring daily or more frequent dosing.

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of HER2, inhibiting the growth of cancer cells that overexpress this receptor. Although it has been successful in treating breast cancers that overexpress HER2, its usefulness in ovarian cancer is limited by a low frequency of overexpression of HER2 in ovarian cancers. In a phase II GOG trial evaluating this agent in patients with recurrent ovarian cancer, only 11% were found to have tumors that overexpressed HER2. The overall response rate in this trial was 7%.[52]

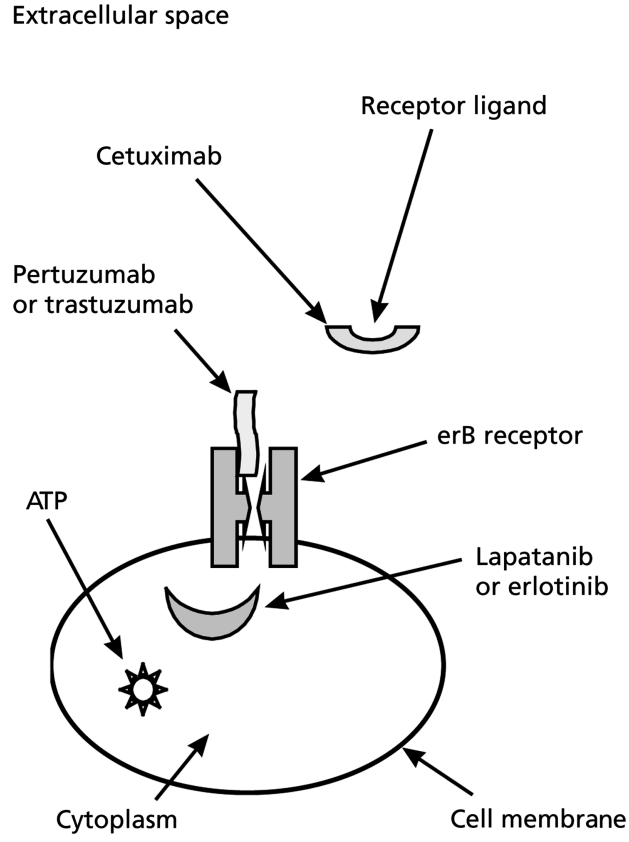

Figure 2 How specific tyrosine kinase inhibitors interfere with erB signaling is shown.

Pertuzumab

Pertuzumab is another recombinant humanized monoclonal antibody that binds to the extracellular domain of HER2.[53] However, it binds at a different epitope from trastuzumab, blocking the dimerization site of HER2. This antibody impairs activity of this receptor even in tumors that do not overexpress HER2. In preclinical studies, it has been shown to inhibit the growth of prostate and breast cancer cell lines that were not inhibited by trastuzumab.[54]

A phase I clinical trial of pertuzumab in patients with advanced solid tumors included 3 patients with ovarian cancer: one who experienced disease stabilization and one who experienced a partial response lasting at least 11 months at the time

of publication.[55] This led to a phase II clinical trial of this agent in heavily pretreated (a median of 5 prior regimens) patients with advanced resistant ovarian cancer. Preliminary data from 117 evaluable patients in this trial showed a partial response rate of 4% and stable disease lasting at least 6 months in 7%.[56] An additional 3% of patients experienced a decline of at least 50% in CA 125 levels. Preclinical data suggested that this agent would have activity in patients whose tumors did not overexpress HER2.[54] In a subset of 28 patients whose tumor samples were evaluated for HER2 activation, results indicated that the pertuzumab had a greater benefit for those whose tumors had high levels of activated HER2.

This agent is also being evaluated in combination with gemcitabine in patients with recurrent ovarian carcinoma. Preclinical data also suggest efficacy for pertuzumab in combination with other targeted agents, such as trastuzumab[57] and erlotinib.[58] The trastuzumab/pertuzumab combination is currently being evaluated in patients with breast cancer.

Cetuximab

Cetuximab is a chimeric human–mouse monoclonal antibody that binds to the EGFR and blocks binding of its ligands, EGF and TGF-α, thereby blocking dimerization and activation.[59] Early phase I studies of cetuximab given as a single agent showed disease stabilization rather than response. However, testing in the phase I setting suggested the agent had greater efficacy when given in combination with chemotherapy.[59] Preclinical data from a mouse xenograft model suggest efficacy using intraperitoneal cetuximab with photodynamic therapy.[60] In light of a recent trial showing a survival benefit from intraperitoneal chemotherapy in patients with ovarian cancer,[61] these preclinical data are intriguing.

Cetuximab is being evaluated in the front-line setting in combination with standard chemotherapy for patients with either optimally debulked or suboptimally debulked stages III and IV disease. Preliminary results recently showed that the regimen has been well tolerated; the first 15 evaluable patients showed a complete clinical response rate of 87%.[62] A trial examining cetuximab as a single agent in recurrent ovarian cancer has just completed first-stage accrual; the data currently are undergoing analysis.

Erlotinib/Gefitinib

Erlotinib is an oral, reversible, selective inhibitor of EGFR. It competes with adenosine 5′-triphosphate (ATP) at the intracellular domain of the EGFR, thereby preventing activation of the receptor.[26] In a recently published phase II study in 34 women with advanced, recurrent ovarian carcinoma who were treated with erlotinib as a single agent, 2 (6%) experienced a partial response and 15 (44%) experienced disease stabilization.[63] Median overall survival was 8 months, and the 1-year survival rate was 35.3%. Interestingly, a positive correlation occurred between the severity of the rash and survival.

Erlotinib is being evaluated in combination with chemotherapy in front-line and recurrent disease. Early results have been presented from 2 front-line phase I studies evaluating erlotinib with standard chemotherapy in patients with advanced disease. Although it was well tolerated with carboplatin and paclitaxel,[64] dose-limiting toxicities were seen with carboplatin and docetaxel, and further data from patients in this trial treated with a lower dose of erlotinib have not yet been presented.[65] A phase II trial of erlotinib in combination with paclitaxel and carboplatin is currently in progress to evaluate efficacy. Additionally, erlotinib is being evaluated for efficacy as maintenance therapy after completion of front-line therapy, and is being evaluated in the phase II setting in combination with bevacizumab in patients with recurrent disease.

A phase II study evaluating gefitinib, another oral inhibitor of EGFR, in patients with ovarian cancer showed limited efficacy.[66] However, translational studies investigating mutations of the EGFR showed that only the patient who experienced a partial response had an activating mutation of EGFR, suggesting that prescreening patients for mutations in EGFR may improve response rates to EGFR inhibitors.

Lapatinib (GW572016)

Lapatinib is an oral, reversible inhibitor of Erb 1 and Erb 2, and is thus a dual-kinase inhibitor.[67] Multiple phase I trials have shown that it is well tolerated and has some efficacy, particularly in the setting of HER2 overexpression.[68–70] It is currently being evaluated as a single agent in patients with recurrent ovarian cancer. It has also been evaluated in combination with paclitaxel in patients with solid tumors and seems to be well tolerated and to have activity.[71] It particularly appears to have activity in women with breast cancer whose tumors were previously resistant to taxanes.

Proteosome Inhibition

The proteasome is a multicatalytic enzyme complex, located in the cytoplasm and nucleus, which is responsible for intracellular protein degradation and recycling (Figure 3). The proteosome regulates cell cycling and apoptosis by removing proteins (e.g., transcription factors) after they undergo ubiquitination. Specifically, the proteasome regulates the cyclin-dependent kinase, NF-κB, which in turn regulates cell adhesion molecules and p53.[72,73] Dysregulation of the proteosome appears to play a role in tumor development, progression, and drug resistance, so inhibition of the proteosome has become a valid target for cancer therapeutics.[74] Pharmacologic inhibitors of the proteasome have shown in vitro and in vivo antitumor activity.[74–77] Preclinical studies show that proteasome inhibition potentiates the activity of other cancer therapeutics, partly through down-regulating chemoresistance pathways.[78,79]

Bortezomib

Bortezomib is the first proteosome inhibitor agent to undergo clinical testing and has been found to have significant efficacy against multiple myeloma and non-Hodgkin's lymphoma.[80,81] Although fewer data are available in the area of solid malignancies, a phase I trial showed promising activity.[82] In light of preclinical data showing that proteosome inhibition can potentiate chemotherapeutics and down-regulate resistance mechanisms, bortezomib was evaluated in combination with chemotherapy in various solid tumors, including chemotherapeutic agents known to have activity in ovarian cancer.[83–86] In a phase I trial in patients with recurrent ovarian cancer, bortezomib was tested in combination with carboplatin and was well tolerated.[87] It is currently being evaluated in combination with carboplatin in patients with recurrent refractory ovarian cancer.

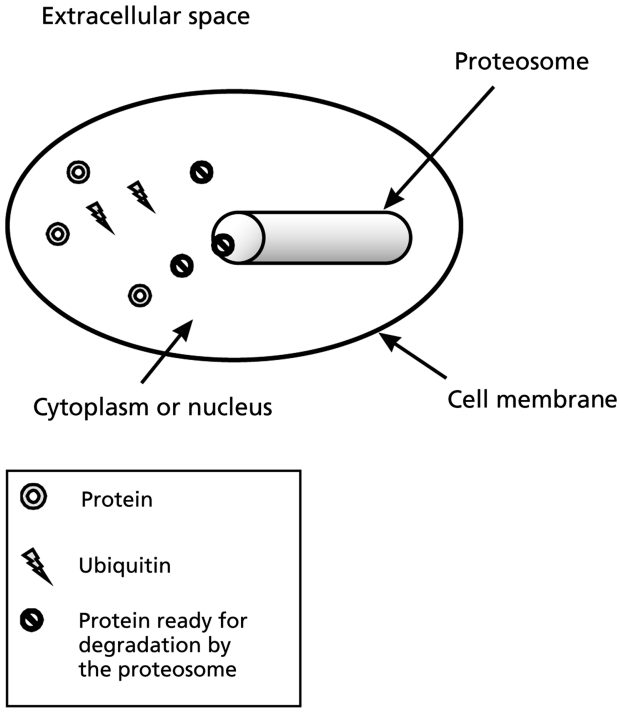

Figure 3 Ubiquitinated protein enters the proteosome. The ubiquitinated protein is degraded, and ubiquitin is recycled for further use by the cell.

The Mitogen-Activated Protein Kinase Pathway

The mitogen-activated protein (MAP) kinase pathway (Figure 4) is involved in regulating cell survival and proliferation and has been shown to be up-regulated in cancer cells. Attempts to control cancer by targeting steps along this pathway have shown some success. Currently, the 2 main approaches are in the area of farnesyl transferase inhibition and Raf inhibitors.

Farnesyl Transferase Inhibitors

Farnesyl transferase activates Ras, which is then able to bind to the cell membrane and activate a signaling cascade that ultimately activates the MAP kinase, leading to cellular activity. The farnesyl transferase inhibitor BMS-214662 has been evaluated in combination with conventional chemotherapeutic agents that are active in ovarian cancer. A phase I trial in patients with advanced solid tumors showed that farnesyl transferase in combination with

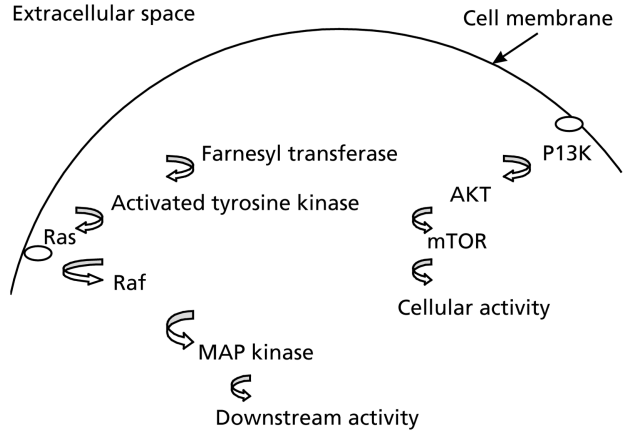

Figure 4 The steps specific to the MAP kinase pathway and the PI3-K/Akt/PTEN pathway are shown. Each of these can be dysregulated in malignancy and can be targets for novel therapies in cancer treatment.

carboplatin and paclitaxel was well tolerated, and that activity seemed to occur.[88] In patients with ovarian cancer, 1 of 2 experienced a prolonged response. A newer agent, lonafarnib (SCH66336), is currently undergoing evaluation in Europe in a phase III trial in combination with carboplatin and paclitaxel as front-line treatment for patients with ovarian cancer, with the comparison arm undergoing standard therapy with carboplatin and paclitaxel.

Raf Inhibition

Raf is a downstream effector molecule activated by signaling from Ras, that in turn continues the cascade and leads to MAP kinase activation.[89] It can also be activated by Ras-independent mechanisms. Inhibition of this target has shown striking success in treating renal cell carcinoma, and sorafenib has recently been approved by the Food and Drug Administration for treating this disease. Phase I studies of sorafenib, a competitive inhibitor of ATP binding to Raf, included patients with ovarian carcinoma, approximately 50% of whom had evidence of stable disease with this drug.[89] This agent is currently being evaluated in the phase II setting in combination with gemcitabine,[90] and with combination carboplatin and paclitaxel in patients with recurrent ovarian cancer. Newer agents that inhibit Raf are being developed but have not reached the stage of phase I testing.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) is a member of the phosphatidylinositol-like kinases and is involved in regulating membrane trafficking and breakdown of proteins, transcription, translation, and maintenance of the cell cytoskeleton (Figure 4). It is regulated by the PI3-K/Akt/PTEN pathway, which is often dysregulated in malignant transformation, typically because of constitutive activation of Akt or upregulation of P13K. This pathway has been shown to be dysregulated in ovarian cancer.[91,92] Rapamycin inhibits mTOR, and analogues of this drug are being studied in the setting of cancer therapy.

CCI-779 (Temsirolimus)

Temsirolimus is a soluble ester of rapamycin and has shown activity both in vitro and in vivo. It has been shown in the phase II setting to have activity in 111 patients with advanced refractory renal cell carcinoma.[93] Median survival in these patients was 15 months. It will soon be tested by the GOG in patients with relapsed ovarian cancer.

RAD 001 (Everolimus)

Everolimus is a rapamycin ester analogue that has been well tolerated in the phase I setting.[94] Although no current trials focus on patients with ovarian cancer, it has shown some activity in other solid tumors, and trials are currently being developed to evaluate this compound and others in patients with relapsed ovarian cancer.

Other Agents

Mab 43.13

Oregovomab is a modified murine monoclonal antibody against CA 125. By binding to this antigen, which is expressed on the surface of most advanced epithelial ovarian carcinoma cells and is also found in the serum, oregovomab activates the immune system to recognize and react against the antibody/antigen complex. Some patients also develop an immune response to tumor cells expressing the CA 125 antigen.[95] In a small trial of 20 patients with recurrent ovarian cancer,[95] oregovomab was well tolerated in combination with various chemotherapy agents and appeared to induce immune responses in a percentage of patients. In this trial, patients who mounted a measurable T-cell response to CA 125 appeared to experience a statistically significant survival benefit.

Oregovomab has been compared with placebo in the front-line setting as consolidation after completion of primary chemotherapy.[96] Although it was well-tolerated, oregovomab did not provide a statistically significant improvement in time to recurrence in this 145-patient study. However, in an unplanned subset analysis, patients with favorable prognostic indicators experienced a statistically significant PFS benefit compared with the placebo group. This agent is currently being evaluated in a larger multi-institutional, placebo-controlled trial as consolidation after front-line therapy for patients with ovarian or primary peritoneal carcinoma and elevated CA 125 levels at diagnosis.

Flavopiridol

Flavopiridol is a semisynthetic derivative of an alkaloid derived from a plant.[97] It works by inhibiting cyclin-dependent kinase and depleting cyclin D1, which coordinate movement through the cell cycle.[98] Flavopiridol has

also been shown to bind to dsDNA.[99] It decreases transcription, blocks angiogenesis, and induces apoptosis. Although its activity as a single agent has been limited since the first phase I trial,[97,98,100,101] it has shown activity in 2 separate phase I trials combined with paclitaxel and cisplatin, respectively. Most notably, some evidence of disease stability was seen.[99,102] It is currently being evaluated in combination with cisplatin in patients with relapsed ovarian or primary peritoneal carcinoma.

Conclusions

As more is learned about the signaling pathways and the micro- and macroenvironments of tumor cells and how they differ from normal cells, new ways to exploit these differences will be found. Newer treatments will be developed to optimize control of cancer while sparing normal cells, making them more effective and less toxic.

Although ovarian cancer is not rare, many novel agents will be evaluated first in the more common cancers, such as lung, breast, and colon cancers, because greater numbers of patients with these diseases can be enrolled in clinical trials. One challenge will be to use the information gained from evaluating these agents in other diseases to determine which are most likely to have activity in ovarian cancer based on knowledge of the pathways that are most important in ovarian cell transformation and disease progression.

How to best evaluate the efficacy of these novel therapies in treating malignant disease will be another challenge. Many of these agents are not cytotoxic, and therefore may have low response rates as single agents using standard response criteria.[103] These new forms of treatment may confer prolonged periods of disease stabilization, an end result that is not typically seen in trials of more traditional cytotoxic agents, but one that ultimately may confer a survival benefit for patients with malignant disease. Experts must ensure that clinical benefit from these agents is appropriately measured so that the evaluation of agents that may help patients live longer is not abandoned.

These targeted therapies have often shown synergy with traditional cytotoxic agents when evaluated in treating malignancy. Preclinical data suggest that targeted therapies may work synergistically with other targeted agents, and the first trials are now evaluating this in patients. Evaluation of combinations of these agents with traditional cytotoxics and other novel agents needs to continue for effective treatments of malignant disease to be found. As the numbers of available novel agents increase, more effective ways to evaluate and predict the combinations that are most likely to affect a particular disease must be developed. This can be accomplished through performing translational research, such as DNA microarrays and proteomic analyses, to see which genes are activated and would serve as the optimal targets for learning about the in vivo effects of these treatments at the molecular level and on the tumor environment.

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