Personalized Care in Uterine Cancer

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Keywords
Endometrial cancer, uterine serous cancers, targeted therapy

Abstract: Endometrial cancer typically presents at an early stage when surgery alone, with or without radiotherapy, is often curative. However, in women who present with advanced disease or who develop disease recurrence, long-term prognosis is poor. While surgical cytoreduction remains the mainstay of initial therapy, over the last several decades, the roles of cytotoxic chemotherapy, radiotherapy, and hormonal therapy have been evaluated in both the adjuvant and recurrent setting in an attempt to improve long-term survival while also minimizing associated toxicities. Unfortunately, response rates remain poor and survival is limited in these settings. More recently, with the introduction of personalized cancer treatment, several biologic agents have been developed that target specific pathways critical to tumor initiation and growth. Molecular studies have found that many endometrial cancers are driven by some of these tumorigenic pathways, which has led to early clinical studies evaluating the role of these targeted agents in patients with advanced or recurrent endometrial cancer. This review describes existing treatment options for patients with early and advanced endometrioid endometrial cancer, as well as for patients with uterine serous cancers. Furthermore, this review examines the growing body of literature involving targeted biologic agents as treatment for patients with advanced or recurrent endometrial cancer.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States. An estimated 46,470 women were diagnosed with uterine cancer in 2011, and it is anticipated that 8,120 of these patients will die of the disease.[1] In contrast to other gynecologic malignancies, the incidence of endometrial cancer has increased in the last several decades.[2] This is, in part, a result of the growing epidemic of obesity.

Currently, women have an overall lifetime risk of 2.53% (1 in 40) of developing endometrial cancer.[1] This cancer can be broadly subdivided into 2 types, based on epidemiologic, histologic, and molecular characteristics. Approximately 80% are Type I (endometrioid) lesions, while the remaining 20% are Type II (non-endometrioid) lesions comprised of more rare histologies: serous,

clear cell, mucinous, or mixed carcinomas.[3] Type I lesions are classically associated with prolonged estrogen stimulation and are usually preceded by atypical endometrial hyperplasia. At presentation, they are often confined to the uterus and are of a lower histologic grade, conferring a more favorable prognosis. In contrast, Type II lesions typically arise in a background of atrophic endometrium, are not associated with estrogen stimulation, and have a propensity for early metastatic spread (particularly serous histology), resulting in a poorer prognosis.

Frequently, women with endometrial cancer present with symptoms such as irregular or postmenopausal vaginal bleeding, allowing for a diagnosis to be made at an early stage when the tumor remains confined to the uterus. In these cases, surgery alone, with or without adjuvant radiotherapy, is often curative, with a 96% 5-year survival for women with disease that is locally confined. However, long-term survival is related to surgical stage at presentation. Women with regional or distant metastatic disease have a poorer prognosis, with 5-year survivals of 68% and 17%, respectively.[1] Furthermore, women with aggressive histologies, such as uterine serous carcinoma (USC), also carry a poor prognosis, with a 5-year overall survival of 46–53%.[4-6] This is largely due to its propensity for early metastatic spread. Up to 55% of patients with USC confined to the inner one-half of the myometrium will have extrauterine metastases, compared to only 17% of patients with high-grade endometrioid carcinoma.[6] Even among patients with no uterine invasion, 37% may have extrauterine disease.[5] Although patients with advanced or recurrent disease often respond to cytotoxic chemotherapy and radiotherapy, response rates are limited (12–42% in the recurrent setting) and provide only a short benefit to progression-free survival (PFS; median, 6 months) or overall survival (median, 12 months).[7,8] As a result, development of novel therapeutic approaches to treating patients with aggressive histologies and advanced or recurrent disease is essential.

Treatment Options

Early-Stage Endometrioid Cancer

Surgical resection, including a total hysterectomy (by laparotomy, laparoscopy, or robotic surgery), bilateral salpingo-oophorectomy, and staging, remains the standard of therapy for early-stage disease. The need for and extent of surgical staging for early-stage disease, involving resection of the pelvic and para-aortic lymph nodes, remains a point of controversy, with evidence to support a variety of practices. Adjuvant radiotherapy has not been demonstrated to improve overall survival in early-stage patients. Radiotherapy reduces the risk of vaginal recurrences and may have a role in targeting occult disease in high-risk patients.

Approximately 5% of endometrial carcinoma cases are diagnosed in women before the age of 40,[9] prompting a conversation regarding fertility-preserving options. Patients with grade 2–3 endometrioid carcinomas or patients with non-endometrioid histologies of any grade are generally not considered candidates for fertility-sparing therapy due to the increased risk for metastasis.[10] Fertility-sparing treatments have centered on the use of oral progestins, such as medroxyprogesterone acetate or megestrol acetate, with durable response rates of up to 58% and a median time to response of 12 weeks. More recently, progesterone-eluting intrauterine devices (IUDs) have been studied to treat low-grade endometrioid carcinomas.[11]

Advanced Endometrioid Cancer

Approximately 10% of endometrial cancer patients are diagnosed with stage III or IV disease.[1] Management for women with advanced stage disease has evolved to primarily include surgical resection followed by adjuvant chemotherapy. Radiation therapy may have a specific role in local control or in treating patients with positive lymph nodes. Surgical resection with the goal to achieve optimal tumor cytoreduction, however, remains the mainstay of initial therapy for advanced disease, and should be performed when feasible. The volume of residual disease following cytoreductive surgery, as well as a patient's age and performance status, appear to be important determinants of overall survival in patients with advanced endometrial carcinoma.[12] Even among patients who have undergone optimal surgery, those with microscopic residual disease survive significantly longer than those with optimal but visible residual disease. Adjuvant chemotherapy with or without radiation is then recommended after surgical debulking. Currently, the most commonly used adjuvant chemotherapeutic regimen is carboplatin and paclitaxel, which was recently reported to be noninferior to the prior standard of paclitaxel, adriamycin, and cisplatin, and is generally better tolerated.[13]

Uterine Serous Cancer (USC)

Adjuvant therapy for early-stage USC remains controversial. While observation alone following surgery has been suggested for early-stage disease,[14] several adjuvant therapies have been attempted in order to reduce the risk of local and distant recurrence. As adjuvant radiotherapy is frequently used to improve local-regional control in early-stage, intermediate-to-high–risk endometrioid cancers, it has been investigated in early-stage USC.[15,16] A retrospective review of the Surveillance, Epidemiology, and End Results (SEER) database identified 1,333 women with either early-stage clear cell (n=451) or

USC (n=882) and found that the median overall survival with surgery alone was 106 months versus 151 months with adjuvant radiotherapy (P=.006).[15] Despite improvements in survival and local-regional control with vaginal brachytherapy and pelvic radiotherapy, there is a concern that radiotherapy alone may not be sufficient to prevent distant recurrence, given the propensity of USC to metastasize to distant sites even at an early stage.[17] Since USC is of a similar histology and behavior to serous carcinoma of the ovary, combination platinum/taxane-based chemotherapy has been used to reduce the risk of distant recurrence. Several studies have demonstrated that combination platinum/taxane-based chemotherapy with or without concurrent radiotherapy for early-stage disease improves recurrence and survival outcomes.[18-20] In a multi-institutional retrospective study of 142 patients with stage I USC, chemotherapy-treated patients experienced significantly fewer recurrences than those not receiving chemotherapy (P=.013).[19] Nevertheless, chemotherapy alone may have its limitations. In a retrospective analysis of 74 stage I USC patients, adjuvant platinum-based chemotherapy was associated with improved disease-free survival (P<.01) and overall survival (P<.05). However, 6 of the 31 (19%) patients who were not treated with vaginal radiotherapy did have local relapse at the vaginal cuff.[21] These findings have led to an increase in the number of patients receiving multimodality adjuvant therapy for early-stage USC.

For treatment of advanced USC, retrospective studies have demonstrated the efficacy of platinum-based chemotherapy in combination with paclitaxel, producing response rates of 89% in the adjuvant setting and 64% in patients treated for recurrent disease, with median progression-free intervals of 13 months and 9 months, respectively.[22] Furthermore, in a prospective phase II study, Ramondetta and associates demonstrated that single-agent paclitaxel is also effective.[23] Twenty patients received paclitaxel 200 mg/m^2 via a 24-hour parenteral infusion every 3 weeks. Among 13 women with measurable disease who received 2 or more cycles of therapy, 10 (77%) had an objective response, including 4 patients who experienced a complete response. The median time to progression was 7.3 months (range, 2–21 months).

Despite these recent findings, there is no clear consensus on the optimal adjuvant treatment strategy for women with USC. Adjuvant treatment for early-stage disease typically includes vaginal cuff brachytherapy and chemotherapy (platinum- and taxane-based). For patients with advanced or recurrent USC, chemotherapy alone is standard. There is a role for directed radiotherapy in patients with stage IIIC disease without ovarian involvement.

Table 1. Genetic Alterations Associated With Type I and Type II Endometrial Carcinomas

Genetic Alteration	Type I Lesions (%)	Type II Lesions (%)
PTEN loss of function[24,44]	83	10
PIK3CA mutation[25,67,68]	36	5
AKT mutation[69,70]	2–4	0
Microsatellite instability[3,68,71,72]	20–30	0–11
KRAS mutation[44,73,74]	15–26	0–5
Nuclear β-catenin[67,75]	25–38	3
TP53 mutation[44,76]	10–17	93
EGFR overexpression[8,77]	46	34
HER-2/neu amplification[58,68]	10	43
FGFR2 mutation[78]	13	2
p16 inactivation[68,76]	10	45

Targeted Therapy for Advanced and Recurrent Endometrial Cancer

Overview

Type I and Type II lesions exhibit distinct molecular alterations (Table 1). Many of these molecular alterations are potential biologic targets with several agents that are currently in development or have proceeded to early clinical trials for various solid tumors (Table 2). With the growing interest in personalizing cancer care by targeting specific molecular aberrations and the limited cytotoxic options available for women with recurrent disease, endometrial cancer is an ideal setting in which to investigate targeted therapies that are under development. The era of targeted therapy also presents other questions that must be addressed. Notably, which patients benefit from a particular agent and how will we be able to best predict response to therapy? In the next few sections, we will review the clinical trials evaluating the efficacy of several agents that have been developed to target specific pathways that are commonly aberrant in endometrial cancer.

PI3K/AKT/mTOR Inhibition

The phosphoinositide-3-kinase (PI3K) pathway is a signal transduction pathway critical to a variety of cellular functions, including cell proliferation and protein synthesis, cell survival, cell cycle progression, cellular metabolism, and angiogenesis. PI3Ks are a family of lipid receptor tyrosine kinases (RTKs) that function by phosphorylating the 3-hydroxyl group of phosphoinositides. The typical initiating event in the activation of PI3K is the binding of a growth factor, such as

Table 2. Completed Phase II Trials of Single-Agent Targeted Therapies for Advanced or Recurrent Endometrial Carcinoma

Drug	Target	Number of Patients	Prior Chemotherapy Regimens	Route	CR (%)	PR (%)	SD (%)
Temsirolimus[27]	mTOR	29	0	IV	0	14	69
Temsirolimus[27]	mTOR	25	1	IV	0	7.4	44
Everolimus[29]	mTOR	28	1–2	PO	0	0	42.9
Ridaforolimus[31]	mTOR	27	0	PO	0	7.7	58
Bevacizumab[47]	VEGF	52	1–2	IV	1.9	11.5	40.4
Thalidomide[51]	VEGF	24	≤1	PO	0	12.5	8.3
Sunitinib[49]	VEGFR	20	≤1	PO	0	15	25
Sorafenib[50]	VEGFR	39	≤1	PO	0	5	49
Erlotinib[54]	EGFR	32	0	PO	0	12.5	46.9
Cetuximab[55]	EGFR	30	≥1	IV	0	5	10
Gefitinib[56]	EGFR	26	1–2	PO	0	4	27
Trastuzumab[59]	HER2	34	No limit	IV	0	0	35.3

CR=complete response; EGFR=epidermal growth factor receptor; HER2=human epidermal growth factor receptor 2; IV=intravenous; mTOR=mammalian target of rapamycin; PO=oral; PR=partial response; SD=stable disease; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor.

epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), or insulin, among others, to its receptor tyrosine kinase (RTK). Activation of PI3K generates phosphatidylinositol 3,4,5-triphosphate (PIP_3) from phosphatidylinositol 4,5-biphosphate (PIP_2). This process is negatively regulated by the tumor suppressor phosphatase and tensin homolog (PTEN) through its lipid phosphatase activity. Loss of PTEN function, either by mutation or epigenetic silencing, occurs in up to 83% of endometrioid cancers, 10% of nonendometrioid cancers, and 55% of precancerous lesions, and has been suggested as an early event in endometrial tumorigenesis.[24] Loss of PTEN results in uncontrolled PI3K activity, which may ultimately lead to cancer. Mutations in PIK3CA, the gene encoding the catalytic subunit of PI3K, are also relatively common and are seen in up to 36% of endometrioid cancers and 5% of nonendometrioid cancers.[25] These mutations also tend to occur in tumors that exhibit loss of PTEN. PIP3 recruits the serine-threonine kinase, AKT, to the plasma membrane, which results in its phosphorylation and subsequent activation. Once AKT is fully activated, it acts as a central node in the PI3K pathway, regulating a wide variety of cellular processes involved with cell survival, protein synthesis, and cellular metabolism.[26] AKT inactivates tuberous sclerosis 1/2 (TSC1/2), which releases its inhibition on the mTOR-regulatory–associated protein of mTOR (Raptor) (mTORC1) complex. Activation of the mTORC1 complex promotes protein synthesis and ribosome biogenesis, as well as subsequent cell proliferation.

Following the discovery that rapamycin had the ability to inhibit mTORC1 signaling, several rapamycin analogues—temsirolimus (Torisel, Wyeth Pharms), everolimus (Afinitor, Novartis), and ridaforolimus—have been developed and evaluated in phase II trials as monotherapy for endometrial cancer. However, at this time, the principal benefit of these drugs has been stabilization of disease. Sequential phase II trials evaluating the efficacy of parenteral temsirolimus in chemotherapy-naïve and chemotherapy-refractory (1 prior regimen) recurrent endometrial cancer demonstrated the single-agent activity of temsirolimus. Among 29 chemotherapy-naïve patients, the partial response rate was 14%, and 69% of patients experienced disease stabilization. In contrast, among 25 patients with chemotherapy-refractory advanced or recurrent endometrial cancer, only 2 (7.4%) patients had a partial response and 12 (44%) had prolonged stable disease.[27] Interestingly, loss of PTEN and expression of phosphorylated mTOR, AKT, or S6K were not significantly correlated with response. Currently, the Gynecologic Oncology Group (GOG) is evaluating the efficacy of temsirolimus in combination with carboplatin and paclitaxel as 1 arm in a 3-arm trial of women with advanced or recurrent endometrial cancer.[28] In a phase II study of 28 patients with advanced or recurrent endometrial carcinoma treated with single-agent everolimus, there were no complete or partial responses, but prolonged disease stabilization was seen in 12 patients (43%) at 8 weeks evaluation and in 6 patients (21%) at 20 weeks evaluation.[29] This was followed by a separate phase II study evaluating the efficacy of everolimus in combina-

tion with letrozole, an oral aromatase inhibitor, in women who have been treated with 1–2 prior chemotherapeutic regimens for advanced or recurrent endometrial cancer. Although this study is ongoing, preliminary results have been encouraging. Of 19 evaluable patients in the first stage of accrual, 4 patients (21%) demonstrated an objective response (1 complete response and 3 partial responses) and 4 patients (21%) had stabilization of disease, which met criteria for second-stage accrual.[30] Finally, oral ridaforolimus produced a 7.7% partial response rate (all in chemotherapy-naïve patients) and a stable disease rate of 58%, with a median duration of 6.6 months.[31] However, significant toxicities were encountered and, as a result, 13 of 33 patients discontinued therapy.

Inhibition of mTORC1 alone has been demonstrated to result in feedback activation of upstream effectors such as AKT.[32] This occurs, in part, by releasing the negative feedback on mTORC2 by S6K. mTORC2 is essential for full activation of AKT. This can lead to resistance to therapy through activation of alternative pathways. As a result, several agents with upstream targets in the PI3K pathway are currently in development or are being evaluated in early clinical trials. Pan-PI3K inhibitors that are currently in phase I or II trials in endometrial cancer include NVP-BKM120,[33] GDC-0941,[34] and XL147.[35] These agents have demonstrated compelling preclinical activity in both cell lines and xenograft mouse models.[36,37] More recently, dual inhibitors of PI3K and mTORC1/2 have been evaluated. NVP-BEZ235 has been shown to be a more potent inhibitor of cellular proliferation and inducer of cell cycle arrest in endometrial cancer cells than everolimus alone.[38] Interestingly, cell lines with KRAS mutations were less sensitive to both agents when compared with wild-type KRAS cell lines. NVP-BEZ235 is currently being evaluated in phase I/II clinical trials in advanced solid tumors and in breast cancer.[39] Other agents in early development that target both PI3K and mTORC1/2 include BGT226 and XL765.

Mutations in AKT are much less common in endometrial cancers, occurring in up to 3% of endometrioid lesions. Given the importance of this signaling protein in many pro-survival and pro-proliferative cellular processes, agents targeting AKT have been developed. MK2206 is an allosteric inhibitor of AKT that is currently being evaluated in several phase I and II trials, including a phase II trial in advanced or recurrent endometrial cancer stratified by PIK3CA mutation.[40]

Another agent that has gained considerable interest is metformin. Metformin is an oral biguanide commonly used in the management of type II diabetes mellitus. Recently, several retrospective and observational clinical studies have reported on the association between metformin and an improvement in cancer incidence and survival in patients with a variety of different cancers. Although the precise mechanism of metformin's antineoplastic activity is not well defined, it has been proposed to involve activation of the liver kinase-B1 (LKB1) and AMP-activated protein kinase (AMPK) pathway. Metformin inhibits mitochondrial respiratory chain complex I, which results in decreased intracellular ATP and an increase in the ratio of intracellular AMP to ATP. This change in the energy status of the cell activates the LKB1/AMPK pathway, in turn phosphorylating TSC2, which results in inhibition of mTORC1 signaling and down-regulation of energy-consuming processes, such as protein synthesis, in an attempt to maintain cellular energy homeostasis. Metformin may indirectly inhibit tumor cell proliferation through its activity on hepatocytes, which results in decreased hepatic glucose secretion and ultimately decreased serum insulin, a known mitogen for a subset of cancer cells. Metformin may also inhibit tumor cell proliferation by directly activating the LKB1/AMPK pathway, thus down-regulating energy-consuming processes, such as protein and lipid synthesis, which are essential for cellular replication. Preclinical studies have demonstrated that metformin is a potent inhibitor of endometrial cancer cell proliferation that is partially mediated by activation of AMPK.[41] Furthermore, metformin may also serve as a chemosensitizer. It was recently demonstrated to potentiate the effects of paclitaxel in endometrial cancer cells through modulation of the mTOR pathway and cell cycle progression.[42] Several ongoing studies in various solid tumors are evaluating the efficacy of metformin as a therapeutic agent. In endometrial cancer, a phase 0 or "window" study is exploring the molecular effects of metformin on endometrial tumors following a short course of treatment prior to hysterectomy.[43] In this study, women diagnosed with endometrial cancer by endometrial biopsy or dilation and curettage are treated with metformin for 2 weeks prior to scheduled hysterectomy. Following the hysterectomy, endometrial tumor tissue before and after metformin treatment will be analyzed to evaluate metformin's effect on its target.

MEK Inhibition

Ras proteins are GTPase binary molecular switches that regulate cell proliferation, differentiation, and survival. Activated Ras can interact with Ras-binding domains (RBDs) on effector molecules, such as PI3K and Raf. The principal effector pathway of Ras is the Raf/MEK/ERK (MAPK) pathway. Mutations in *KRAS* result in constitutive activation that leads to uncontrolled signaling through effector pathways. *KRAS* mutations have been found in up to 26% of endometrioid lesions and 5% of nonendometrioid lesions.[44]

Given the relatively high prevalence of *KRAS* mutations in endometrial cancer, particularly Type I lesions, this pathway has also been explored as a potential target

for small molecule inhibitors. The most well-developed drug in this setting is AZD6244 (selumetinib), an inhibitor of MEK1/2. The GOG opened a phase II trial of AZD6244 in patients with advanced or recurrent endometrial cancer treated with 1–2 prior chemotherapeutic regimens.[45] This trial was estimated to accrue up to 54 patients, but is currently closed. However, it is important to note that both the Ras/Raf/MEK and PI3K pathways appear to be highly integrated with significant cross-talk, including cross-inhibition and cross-activation.[26] As a result, inhibition of one pathway may lead to activation of the other, such as that observed with MEK inhibitors and AKT activation in preclinical studies.[46] Thus, it is becoming increasingly evident that strategies aimed at targeting multiple signaling pathways will be needed moving forward.

Angiogenesis Inhibition

Angiogenesis, or new vessel formation, is essential to the growth and development of various solid tumors, including endometrial carcinoma. Overexpression of vascular endothelial growth factor (VEGF) promotes increased vessel formation and proliferation, which improves delivery of oxygen and nutrients to the tumor, facilitating its growth. As a result, the VEGF ligand and its receptors have been proposed as possible therapeutic targets. In a phase II study completed by the GOG, 53 women with advanced or recurrent endometrial carcinoma who had received no more than 1–2 prior cytotoxic chemotherapeutic regimens were treated with single-agent bevacizumab (Avastin, Genentech), a monoclonal antibody directed against the VEGF ligand. Although the overall response rate was modest (13.5%), an impressive 40.4% of patients demonstrated PFS at 6 months, and therapy was generally well tolerated.[47] To date, bevacizumab has been the most active targeted agent administered as monotherapy in the GOG-229 queue, which includes a series of phase II trials investigating the efficacy of several biologic agents for advanced or recurrent endometrial cancer. Aflibercept (Eylea, Regeneron) is a fusion protein containing the extracellular domains of VEGFR1 and VEGFR2. It functions as a decoy receptor and binds circulating VEGF, preventing its interaction with cellular receptors. In a phase II trial of recurrent endometrial cancer patients, aflibercept produced a response rate of 7% and a 6-month PFS of 41%; however, it was associated with gastrointestinal and hematologic toxicities.[48]

Attempts to target the VEGF receptor (VEGFR2) directly with 2 multi-RTK inhibitors (sunitinib [Sutent, Pfizer] and sorafenib [Nexavar, Bayer]) have resulted in limited success. In a phase II trial of women with advanced or recurrent endometrial cancer, sunitinib produced a partial response rate of 15%, with disease stabilization in an additional 25% of patients.[49] In a separate phase II trial, sorafenib produced fewer responses (partial response rate of 5%); 50% of patients had stabilization of disease at 2 months of therapy, but this decreased to 11% at 4 months.[50] Finally, the GOG also assessed the efficacy of thalidomide (Thalomid, Celgene), an agent with anti-angiogenic properties, as monotherapy in women with advanced or recurrent endometrial cancer.[51] The precise mechanism of thalidomide's anti-angiogenic activity is unknown. In this study, overall responses were poor, with only 12.5% of patients achieving a partial response and an additional 8.3% demonstrating stabilization of disease. The median PFS and overall survival were 1.7 months and 6.3 months, respectively. As with many of these targeted therapies, the utility of VEGF and VEGFR inhibitors is still being evaluated in combination with cytotoxic chemotherapy or agents targeting other pathways.

EGFR and HER2 Inhibition

The EGFR family includes 4 cell surface receptors—EGFR (HER1), HER2, HER3, and HER4—which, upon ligand binding, signal through a variety of effector pathways (such as PI3K and Ras/Raf/MEK) to promote cell proliferation and survival. EGFRs are also expressed on endothelial cells within the tumor microenvironment, promoting endothelial cell proliferation and angiogenesis.[52] EGFR overexpression is commonly encountered in endometrial cancer, regardless of histology; however, recent evidence indicates that this is not sufficient to predict response to therapy.[53] As such, small molecule inhibitors of EGFR have had only limited success in endometrial cancer. In a phase II study of women with advanced or recurrent endometrial cancer who had not received prior chemotherapy, erlotinib (Tarceva, Genentech/Roche) produced an overall response rate of 12.5% and a stable disease rate of 47%, with a median duration of 3.7 months.[54] Fluorescent in situ hybridization (FISH) demonstrated no correlation of response with EGFR gene amplification. Cetuximab (Erbitux, ImClone) is a chimeric human/mouse monoclonal antibody that competitively inhibits the activity of EGF by binding to the extracellular domain of the EGFR. While cetuximab has been used in the treatment of colorectal and head/neck cancers, it produced only a partial response rate of 5% and stable disease rate of 10% in a phase II study including women with heavily pretreated advanced or recurrent endometrial cancer.[55] Finally, gefitinib (Iressa, AstraZeneca), which binds to the ATP binding site of EGFR, was also evaluated by the GOG in a phase II trial of women with advanced or recurrent endometrial cancer who had received up to 2 prior chemotherapeutic regimens. In this trial, gefitinib produced a partial response rate of 4% and a stable disease rate of 27%.[56] While responses to EGFR

inhibitors have been modest at best, it is also important to note the role that other molecular alterations may have had on their effectiveness. In colorectal cancer, the presence of KRAS mutations has been significantly associated with lack of response[57] to the point that KRAS mutation analysis of tumors is now recommended for potential candidates considering anti-EGFR therapy. As KRAS mutations are encountered in up to 30% of Type I endometrial cancers, this remains an important concept moving forward in the study of this class of drugs in patients with endometrial cancer.

Aberrant expression of *ERBB2*, the proto-oncogene that encodes for HER2, is commonly encountered in Type II (non-endometrioid) endometrial cancers. Overexpression and amplification of HER2 occurs in 43% and 29% of serous carcinomas, respectively.[58] Given this frequency, trastuzumab was evaluated as monotherapy by the GOG in a phase II study that included patients with advanced or recurrent, HER2-positive endometrial cancer. Unfortunately, trastuzumab did not demonstrate activity, producing no objective responses and a median PFS and overall survival of only 1.85 months and 7.85 months, respectively.[59] Lapatinib (Tykerb, GlaxoSmithKline), a dual RTK inhibitor of EGFR and HER2, has also been studied in endometrial cancer,[60] although results have not yet been reported.

PARP Inhibition

Increased poly (ADP-ribose) polymerase (PARP) activity is one mechanism by which tumor cells avoid apoptosis caused by DNA damage. Cells are capable of repairing damaged DNA through several mechanisms. PARP activity is essential for the repair of single-stranded DNA breaks through the base excision repair (BER) pathway.[61] Over the last several years, compounds that inhibit PARP have been developed and studied for their use as anticancer therapy, particularly in patients with *BRCA1* or *BRCA2* mutations. When PARP is inhibited, the cell loses its capacity to repair single-strand DNA breaks (SSBs). Unrepaired SSBs eventually result in double-strand breaks (DSBs) during DNA replication. While DSBs are normally repaired by homologous recombination (HR), cells with a defect in HR are incapable of repairing DNA effectively. This leads to genetic instability and eventual cell death, a concept known as synthetic lethality. While much of the existing literature has focused on PARP inhibition in BRCA-associated cancers, another potential synthetic lethal approach has been to combine PARP inhibition with PTEN loss. Recent studies have suggested that PTEN may be involved in the HR DNA repair pathway through transcriptional regulation of RAD51 and/or RAD51 localization to the nucleus upon DNA damage.[62,63] RAD51 plays an important role in HR DNA repair. Thus, decreased expression of RAD51 or defects in translocation to the nucleus due to PTEN loss results in defective HR DNA repair. A recent study demonstrated that cells with loss of PTEN function displayed a 5-fold reduction in HR DNA repair when compared to isogenic PTEN wild-type cells.[62]

Given the high frequency of PTEN loss of function in Type I (endometrioid) lesions with a subsequent deficiency in HR DNA repair, this may be a promising target for PARP inhibition. Preclinical data have demonstrated that PTEN deficiency sensitizes cells to PARP inhibition when administered as monotherapy. In human endometrial cancer cell lines, PTEN-deficient cells treated with the PARP inhibitor KU0058948 were shown to display significantly fewer RAD51 foci and decreased survival.[63] These promising results were carried into an in vivo xenograft model using a PTEN-deficient human colorectal cancer cell line (HCT116). In this model, PARP inhibition suppressed tumor growth when compared with vehicle control. While there has been limited experience with PARP inhibition in human PTEN-deficient endometrial carcinoma, Forster and coworkers recently presented a case report of a patient with recurrent PTEN-deficient endometrioid endometrial adenocarcinoma who demonstrated significant clinical benefit when enrolled on a phase I trial using the PARP inhibitor olaparib as monotherapy.[64] However, prospective human studies are necessary to further investigate the role of PARP inhibitors in PTEN-deficient endometrial cancer.

FGFR2 Inhibitors

Fibroblast growth factor receptor-2 (FGFR2) is an RTK that binds fibroblast growth factor (FGF) and mediates cell division, growth, and differentiation. Mutations in *FGFR2* occur in up to 16% of type I tumors and 2% of type II tumors, and cause constitutive activation of the FGFR2 RTK, resulting in persistent signaling through its effector pathways, including PI3K. Dovitinib, an oral inhibitor of FGFR and VEGFR, is being evaluated in a phase II trial of patients with advanced or recurrent endometrial cancer, stratified by *FGFR2* mutation status.[65] The GOG is currently evaluating the efficacy of brivanib, another FGFR and VEGFR inhibitor, in a phase II study of unselected advanced or recurrent endometrial cancer.[66] Once data are available for these studies, we will have a better understanding of the role of FGFR2 inhibitors in endometrial cancer.

Conclusions and Future Directions

While patients with early-stage endometrial cancer have an excellent prognosis with standard surgical resection

with or without adjuvant radiotherapy, identifying patients who will benefit from full lymphadenectomy and defining the role of adjuvant treatments in high-risk patients will help maximize cures and minimize complications. However, the principal unmet need in the treatment of endometrial cancer centers on patients who present with progressive or recurrent disease for whom conventional therapies are limited and only produce modest, short-lived responses. As we move forward in evaluating the efficacy of targeted agents, we must consider that genetic alterations do not occur in a vacuum. Instead, molecular pathways are frequently interconnected, and multiple aberrations can occur simultaneously in a given tumor. To date, a majority of phase II studies in patients with endometrial cancer have used targeted agents as monotherapy without first screening for and stratifying by molecular aberrations. It is becoming increasingly clear that, due to the complexity of the molecular pathways and the number of different genes and proteins that can be altered, single-agent targeted therapy is unlikely to be the solution. Instead, trials evaluating combinations of agents that target different pathways need to be developed to improve response rates and response durations. While many of the earlier phase II studies did not preselect endometrial cancer patients by molecular or genetic aberration, the concept of preselecting patients has been gaining interest and, when incorporated into clinical studies, will hopefully improve responses. To do this, it is essential that current trials incorporate translational endpoints to identify and evaluate biomarkers in an effort to evaluate the sensitivity of tissues to the targeted agent and improve our capabilities to predict response to therapy.

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