Targeted Therapies in Endometrial Cancer

Endometriyum Kanserinde Targeted Terapiler

Targeted Terapiler / Targeted Therapies

Selen Dogan, Nasuh Utku Dogan
Akdeniz University, Department of Obstetrics and Gynecology, Antalya, Türkiye

Özet

Endometriyum kanseri gelişmiş ülkelerde en sık görülen genital kanserdir. Genellikle erken evrede tanı alır ve iyi prognozludur. İleri evre hastalıkların ve nükslerin yönetimi ise güçtür. Endometriyum karsinogenezinde de diğer kanserlerdeki gibi bazı sık görülen genetik değişiklikler mevcuttur. Her bir birey için en uygun tedavinin seçilmesi anlamına gelen kişiselleştirilmiş tıp son yıllarda hastaların klinik bakımında dikkat çekmektedir. Targeted terapiler kişiselleştirilmiş tıpın bir parçası olarak gelişmiştir ve spesifik olarak tek bir hedefe ya da biyolojik yolağa etki ederler. Endometriyum kanserinde, targeted terapilerin hedefi olabilecek PTEN tümor supresör geni, DNA mismatch onarım genleri, PI3K/AKT/mTOR yolağı ve p53 onkogeni gibi bir çok gende moleküler değişiklikler mevcuttur. Son yıllarda targeted terapiler over kanseri hastalarında klinik uygulamalar kazanmaktadır. Yakın gelecekte yeni ilaçların geliştirilmesi ile bu ilaçlar endometriyum kanserinde de primer hastalık ve nükslerin rutin klinik uygulamarında kullanılmak üzere marketlerde yerini alacaktır.

Anahtar Kelimeler

Endometriyum Kanseri; Kemoterapi

Abstract

Endometrial cancer is the most common genital cancer in developed world. It is generally diagnosed in early stage and it has a favorable prognosis. However, advanced staged disease and recurrences are difficult to manage. There are some common genetic alterations related to endometrial carcinogenesis in similar fashion to other cancers. Personalized medicine, which means selection of best suited treatment for an individual, has gain attention in clinical care of patients in recent years. Targeted therapies were developed as a part of personalized or "tailored" medicine and specifically acts on a target or biologic pathway. There are quite a number of molecular alteration points in endometrial cancer such as PTEN tumor suppressor genes, DNA mismatch repair genes, PI3K/AKT/mTOR pathway and p53 oncogene which all might be potential candidates for tailored targeted therapy. In recent years targeted therapies has clinical application in ovarian cancer patients and in near future with the advent of new agents these "tailored" drugs will be in market for routine clinical practice in endometrial cancer patients, in primary disease and recurrences as well.

Keywords

Endometrial Cancer; Chemotherapy

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Corresponding Author: Selen Doğan, Akdeniz University, Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncologic Surgery Antalya,Turkey. T.: +90 2422496000 E-Mail: selendogan@akdeniz.edu.tr

Introduction

Endometrial cancer (EC) is the sixth most common cancer among women worldwide, 287,000 new cases were diagnosed and 74,000 of them were died from disease worldwide each year [1]. Epidemiologically, EC has been classified into two groups. The two groups differ in incidence, molecular pathophysiology, hormone dependence and clinical behavior. Estrogen dependent type 1 is characterized by endometrioid histology, low grade and stage disease and favorable prognosis. Type 1 cancer comprises majority of the whole group (approximately 80%). Estrogen non-dependent type 2 endometrial cancer is associated with non-endometrioid histology, a higher grade and advanced stage disease and a poorer prognosis[2]. A range of genetic abnormalities are encountered in endometrial cancer. Approximately 90 % of cases occur sporadically, whereas remaining 10% of cases have hereditary origin [3]. EC typically presents with abnormal uterine bleeding. Thanks to early bleeding in the course of disease, most of the patients are diagnosed at an early stage and advanced or recurrent disease is relatively uncommon. Overall 5-year survival rates for each stage according to the FIGO 2009 staging system were reported as follows: 89.6% in stage 1a disease, 73.5 % in stage 2 disease and 56.3-49.4 % in stage 3a-3c2 disease. The prognosis for most women with disease limited to the uterus (stage 1) is excellent[4].

Treatment of patients with EC is primarily based on surgery. Hysterectomy with bilateral salpingooopherectomy constitutes the first step and lymphadenectomy is subsequently performed to complete the surgical staging [5]. Adjuvant cytotoxic chemotherapy and radiotherapy also may be administered in selected patients whenever required. Hormonal therapy with tamoxifen, progestins and aromatase inhibitors are alternative treatment modalities in advanced stage endometrial cancer [6]

Personalized medicine, which means selection of best suited treatment for an individual, has gain attention in clinical care of patients in recent years. Targeted therapies were developed as a part of personalized or "tailored" medicine and specifically acts on a target or biologic pathway , which in case of inactivation, blocks malignant or pathologic process and have a potential to be used in rheumatologic , oncologic, and endocrine diseases.

Targeted therapy in oncology

Standard cytotoxic chemotherapy specifically selects rapidly dividing normal and malignant cells. Conversely, targeted therapy blocks the proliferation of cancer cells by interfering with specific molecules required for tumoral development. If targeted therapy used in combination with chemotherapy, efficacy is increased for many types of cancer. Examples of this type of targeted therapy include hormonal based therapies in breast and prostate cancer; small-molecule inhibitors of the EGFR pathway in lung, breast, and colorectal cancers; blockers of invasion and metastasis enabling proteins and enzymes; antiangiogenesis agents; proapoptotic drugs; and proteasome inhibitors.

The ideal cancer target can be defined as a molecule, essential for malignant phenotype and is not expressed significantly in other normal tissues. Also clinical response should be observed in a majority of patients whose tumors express the target and minimal responses in patients whose tumors do not express the target. Targeted therapy is often used in addition to, rather than in place of traditional chemotherapy. Thus financial burden of these treatments gets governments into a confusion regarding routine use of this drugs in national health programs .

Molecular alterations in endometrial cancer

PTEN: Tumor suppressor gene, PTEN (phosphatase and tensin homolog deleted on chromosome ten) encodes phosphatase which antagonizes PI3 kinase/AKT signaling. PTEN mutations are common in type 1 EC and were reported to be present in up to 83% of carcinomas and 55% of precancerous lesions [7] . Decreased activity or loss of function in PTEN affects cellular proliferation and survival and finally leads to decrease in cell adhesion and hence cellular migration follows [8].

PI3K/AKT/mTOR pathway : PIK3CA is the catalytic subunit of PI3K. Mutations in this gene occur in 24-36% of all cases and are coexistent with PTEN mutations in 14–26% of cases [9]. PIK3CA also plays an important role in the PI3K/AKT regulatory pathways of apoptosis (figure 1). Activation of this pathway suppresses apoptosis that is triggered by various stimuli. PI3K is supposed to be a potential candidate target for future trials and therapies[10] .

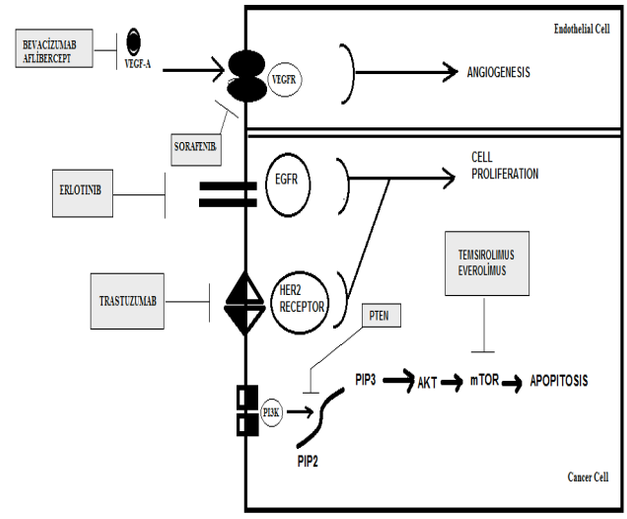


Figure 1. Some common pathways in endometrial carcinogenesis and their corresponding "targeted" drugs.

DNA mismatch repair genes and microsatellite instability: DNA repair and mismatch repair system (MMR) play a critical role in promoting genetic stability. Microsatellites are simple, repetitive DNA sequences in the genome, which are susceptible to replication errors. Microsatellite instability (MSI) is observed whenever there is a defect in intact DNA during repair or duplication process. These defects are all related to mutations or faulty mismatch procedure in MMR genes[11]. Most of the MMR deficiencies underlying MSI in EC seems to involve epigenetic inactivation or silencing mechanisms. The most commonly observed cause of MSI in sporadic endometrioid EC is the inactivation of MLH-1 by hypermethylation of CpG islands in its promoter [12] .

Kras-Braf : The K-ras gene encodes a cellular membrane GTPase and acts as a molecular switch during cell signaling. This function has been largely related to tumor growth and differentiation. Mutations of this gene have been identified in 19–46% of ECs[12] .

HER2/neu and EGFR : HER-2/neu ,also called erbB2 or HER2, is a member of the receptor tyrosine kinase (RTK) family, which is involved in cell proliferation via two downstream signaling

pathways: the Ras-Raf-MAP kinase pathway and the phosphatidyl inositol-3-kinase (PI3K) downstream protein serine/threonine kinase pathway (AKT)[13] . Over-expression of the protein product of HER-2/neu is reported in 9–30% of all ECs, particularly in non-endometrioid tumors [14].

Wnt/B-catenin/E-cadherin: The beta-catenin gene is a component of the E-cadherin-catenin unit, which is very important for cell differentiation and the maintenance of normal tissue architecture. This unit also plays an important role in signal transduction. It becomes evident that E-cadherin, b-catenin, and WNT signalling pathway also contribute to control of the complex morphogenetic process of epithelial to mesenschimal transition. Loss of E-cadherin expression leads to a reduced degradation and subsequent overexpression of free cytoplasmic b -catenin, which can exert its own nuclear function without control [15].

TP53:After DNA damage, tumor suppressor gene p53, encodes p53 protein and p53 accumulates in the nucleus, initiates cell cycle arrest by inhibiting cyclin-D1 phosphorylation of the Rb gene and finally this leads to apoptosis[16]. Mutations in the p53 tumor suppressor oncogene are present in approximately 90% of all tumors and constitute the most common genetic alterations in Type II ECs. Conversely p53 mutations have been observed in only 17% of the cases of endometrioid EC[17] .

Targeted therapies in endometrial cancer

PI3K/AKT/mTOR pathway inhibitors

Mammalian target of rapamycin (mTOR) is an intracellular serine-threonine kinase protein. It acts as an antiapoptotic factor by inhibiting G1 arrest action by affecting several signaling pathways including VEGF, ILGFR and PI3K-akt [18] . An intravenous mTOR inhibitor Temsirolimus was developed and studied in phase II trial of metastatic and/or locally advanced recurrent endometrial cancer. This study showed 4 % PR (partial response) and 48% SD (Stabile disease) with a median duration of 4.3 months in chemotherapy treated group, %14 PR and 69% SD with a median duration of 5.1 months in chemotherapy naive group[19].

Everolimus an oral mTOR inhibitor also was studied in phase II trials in patients with recurrent endometrial cancer previously treated with chemotherapy and prolonged (>8 weeks) SD rate was 43%[20]. In another multicenter phase II study, patients with advanced or metastatic endometrial cancer refractory to one or two previous chemotherapy regimens received everolimus 10mg per day. The 3-month non-progressive disease rate was 36 % and PR was 5% [21] .

Other mTOR inhibitor Ridaforolimus also presents some activity against endometrial cancer. In a multicentre, phase II trial, single agent ridaforolimus has antitumor activity and acceptable tolerability in advanced endometrial cancer patients[22] .

There are studies evaluating effects of mTOR inhibitors in combination with hormonal agents, standard chemotherapeutics or with other targeted molecules. In a phase II trial, according to both objective tumor response and PFS (progression free survival) at six months, combination of temsirolimus and bevacizumab has an activity against recurrent or persistent endometrial cancer. However, this treatment regimen was associated with significant toxicity[23]. Adding further combination of megestrol acetate and tamoxifen to temsirolimus therapy did not augment activity and the combination was associated with an increased risk of venous thrombosis[24].

HER2 and Epidermal growth factor receptors (EGFR) inhibitors

Epidermal growth factor receptor (EGFR) inhibitor is an agent which reacts to inhibit EGFR on cancer cells . EGFR effects three major signaling pathway: The Ras/Raf/MEK/ERK pathway, the PI3K-Akt pathway, the JAK/STAT pathway. Anti-EGFR monoclonal antibodies (Cetuximab) and small molecule TKI's (Gefitinib, Erlotinib, Lapatinib) are the two classes of EGFR inhibitors. All of these pathways work for different critical functions in the cell. A phase II study was performed to evaluate single agent activity of an oral EGFR inhibitor erlotinib in patients with advanced, recurrent disease who were chemotherapy naive and had previously received hormonal therapy. In this study PR was 12.5% and SD was 47% [25] .

Gefitinib was also studied in a phase II trial with 29 patients but only one patient showed complete response[26].

A phase II trial was performed to evaluate the efficacy and safety of lapatinib in 30 patients with persistent or recurrent endometrial cancer. Merely, three patients had PFS<6 months, one had a partial response, seven had stable disease and 21 had progressive disease. According to results of this study Lapatinib showed limited activity without patient selection for spesific mutation [27].

After the success in mutation positive breast cancer, trastuzumab was studied in endometrial cancer. Unfortunately as a single agent, trastuzumab did not demonstrate any activity against endometrial carcinomas with HER2 overexpression or HER2 amplification in phase II trial [28].

Angiogenesis inhibitors

Vascular endothelial growth factor (VEGF) is the most important growth factor responsible for angiogenesis[29]. There are two groups of angiogenesis inhibitors targeting VEGF pathway: Direct VEGF blockers and multitargeted tyrosine kinase inhibitors which are directed against VEGF receptors.

Bevacizumab, a recombinant humanized monoclonal antibody, antiVEGF-A, is approved by the U.S. FDA (Food and Drug Administration) for various cancer including metastatic colorectal, non-small cell lung, renal cell, and breast cancers. A Phase II, GOG 229 trial enrolled 52 patients with persistent or recurrent endometrial cancer previously receiving cytotoxic regimens. Single agent bevacizumab shows 13.5% clinical response in seven patients (1 complete, 6 partial response). Twenty-one patients (40.4%) survived with progression free of the tumor for at least 6 months. Median PFS and overall survival times were 4.2 and 10.5 months respectively [30].

Thalidomide as an antiangiogenic agent was studied in a phase II trial of patients with persistent or recurrent endometrial cancer refractory to cytotoxic chemotherapy. Due to limited ability to delay progression (as measured by PFS at 6 months) or produce objective responses, thalidomide did not considered as an active agent in refractory endometrial cancer [31].

Aflibercept (VEGF-Trap) is an IgG recombinant fusion protein against VEGF. Aflibercept was studied in a phase II trial with 44 patients in recurrent or persistent endometrial cancer. In this study, PFS rate at 6 months was 41%, three patients (7%) had PR and median PFS was 2.9 months. However, aflibercept was associated with significant toxicity including two treatment related deaths (gastrointestinal perforation and pulmonary embolism)[32]

Tyrosine kinase receptor inhibitors

Sorafenib a multitargeted kinase inhibitor has antiangiogenic activity as well. This agent has been studied in patients with

advanced uterine carcinoma and carcinosarcoma [33]. A multiinstitutional, non-randomized phase II trial recruited 40 patients with uterine carcinoma. Two (5%) patients had PR and 17 (42.5%) achieved SD. No patients with carcinosarcoma had an objective response. Sorafenib shows minimal activity in patients with uterine carcinoma [33].

Another inhibitor Sunitinib, targeting multiple receptor tyrosine kinases including VEGFR was also studied in a phase II trial with 30 patients. Sunitinib produced PR in three patients (ORR:15%) and SD in 5 patients , 4 of these patients remained progression free 6 months. Median time to tumor progression was 2.53 months in previously treated patients with recurrent/metastatic endometrial cancer [34].

Poly(AD P-ribose) polymerase inhibitors

PARP catalyzes the polyADP ribosylation of proteins which participate in DNA repair. Inhibitors of PARP were shown to be highly selective for cancer cells which have homologous recombination deficiencies, such as BRCA1 or BRCA2 genes mutations[35]. PTEN deficiency may cause DNA repair homologous recombination defect causing sensitivity to poly ADP-ribose polymerase (PARP) inhibitors in cancer cells[36] . PARP inhibition may be useful in endometrial cancer, particularly type 1 endometrioid type cancer which is highly associated with PTEN mutations and deserves further attention.

Conclusion

Endometrial cancer is generally diagnosed in early stage and it has a favorable prognosis. However advanced staged disease and recurrences are difficult to manage. Improved knowledge about molecular basis of endometrial cancer has led to the designation of molecular targets for novel therapeutic strategies of treatment. In recent years targeted therapies has clinical application in ovarian cancer patients and in near future with the advent of new agents these “tailored” drugs will be in market for routine clinical practice in endometrial cancer patients, in primary disease and recurrences as well. Another point is need for identification of these biomarkers that predicts sensitivity to targeted therapies. When these follow-up markers are available we will have more precise knowledge regarding the real efficacy of targeted therapies.

Competing interests

The authors declare that they have no competing interests.

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