Emerging targeted agents in endometrial cancer treatment

E Timotheadou*

Abstract

Introduction
Management of recurrent or metastatic endometrial cancer remains an area of active research; however, for majority of patients, treatments do not offer significant benefits and prognosis remains poor. The progress made in understanding the molecular mechanisms of tumourigenesis and metastasis in the subtypes of endometrial cancer has led to the identification of molecular targets and intensified efforts to obtain active therapeutic agents. Currently, there are several new molecules going through different stages of clinical development, which will hopefully improve treatment outcomes in the following years. These new molecules can be used either as single agents or in combination with chemotherapy. This short review focuses on the most recently published data.

Conclusion
The need for more effective treatments in recurrent endometrial cancer offers significant motivation for testing new agents in this group of patients. The identification of specific gene mutations or target molecules remains the focus for ongoing research. Data gathered from research and analysis of combination of approved drugs like bevacizumab with novel agents offers hope, and, currently, angiogenesis seems to be one of the more active areas of research in gynaecologic oncology in general and more specifically in endometrial cancer.

Introduction
Endometrial cancer is the most common gynaecologic malignancy. In recent years, a significant amount of new data gathered has facilitated a more accurate histologic classification consisting of two molecularly distinct subtypes. Type I, endometrioid histology, is the most common in numbers, correlates with oestrogen abundance and often has a favourable prognosis. Type II includes serous papillary or clear-cell tumours and is less frequent and shows more aggressive characteristics and low dependency on oestrogens.

Type I includes about 80% of all endometrial cancers and has been increasing in numbers in correlation with the use of oestrogen-only replacement therapies. Anovulation, nulliparity, early menarche and obesity have also been identified as risk factors. It is characterised by several molecular changes that make their appearances in the course of tumour progression. Most frequently seen alterations include microsatellite instability (MSI), phosphatase and tensin homolog gene (PTEN), K-Ras and β-catenin gene mutations. The MSI phenotype appears in 20% of Type I cases and includes inactivation of any of the proteins or genes that are included in the mismatch repair process: MLH1, MSH2, MSH3 and MSH6.

In endometrial cancer, the most common event in the MSI mechanism is the inactivation of MLH1 caused by hypermethylation of the CpG islands that leads to epigenetic silencing of the gene promoter. Less frequently seen are the MSH6 mutations and MSH3 frame shift mutations. The presence of MSI may facilitate further molecular changes, through inactivation of genes with susceptible repeat elements like TGF-β1 receptors and IGFIIR, thus producing new tumour clones with enhanced invasive and metastatic potential. In addition, these tumours present a higher frequency of K-Ras mutations, which appear in about 30% of all Type I cases.

The β-catenin gene is located in 10q23 chromosome and its inactivation is most common in Type I tumours, appearing in more than 80% of cases that have developed tumours following a pre-malignant diagnosis. Loss of heterozygosity due to mutations or deletions is common, as is the complete inactivation of both alleles. The main PTEN activity is expressed by a lipid phosphatase that converts inositol triphosphate to inositol biphosphate and therefore inhibits the signal transduction pathways regulated by the inositol triphosphate. Endometrial MSI tumours have more deletions, including at least three base pairs, and this group has very low incidence of mutations in the polycystin repeat of exon 4.

The β-catenin is part of the E-cadherin unit of proteins and plays a critical role in cell differentiation, maintenance of tissue architecture and Wnt signal transduction pathway. Type II endometrial cancer is usually of serous papillary or clear-cell histology and is unrelated to oestrogen exposure and often arises in previously atrophic endometrium.
most common molecular alterations observed are p53 and p16 mutations, Her-2 overexpression or amplification and loss of E-cadherin.

The p53 mutations appear in almost 90% of Type II cases. The mutated p53 produces a non-functional protein that acts as a double-negative inhibitor of the wild-type p53 and, as a result, DNA-damaged cells avoid apoptosis and survive further. Also, p53 mutations are identified in about 80% of endometrial intraepithelial carcinomas, which are considered to be the precursor lesions to the serous carcinoma development.

The p16 gene is located in 9p21 and encodes a cycle regulation protein. Inactivation by mutation results in uncontrolled cell proliferation and has been described in 45% of serous carcinomas and less often in clear-cell ones.

Her-2/neu is an oncogene that belongs to the EGFR family and encodes a transmembrane receptor with tyrosine kinase activity and has a critical role in signal transduction pathways in many different tumours. Specific anti-HER2-targeted therapies have been in use for years in early and advanced breast cancer and, more recently, in advanced gastric adenocarcinoma. In serous endometrial adenocarcinomas, Her-2 overexpression has been reported in 45% of the cases and amplification in 70% of the cases.

E-cadherin is a transmembrane protein with five extracellular domains and one intracellular domain that connects to the actin cytoskeleton. Reduction or loss of E-cadherin results in reduced cell-to-cell cohesion and increased cell motility. This event is more commonly seen in non-endometrioid tumours of low differentiation and poorer prognosis.

Following progress made in understanding several pathways of angiogenesis, cell proliferation and survival, signal transduction, genetic alterations and development of various targeted agents, endometrial cancer, among other solid tumours, has also been the field of active research in recent years. Literature has already included a large number of basic and clinical research publications, but contribution to the routine clinical practice has been limited. Recurrent endometrial cancer remains an incurable disease, with limited treatment options, short progression-free intervals and poor overall survival for a significant number of patients. However, the concept of targeted treatments remains active and there are various agents that are currently under investigation in endometrial cancer, assessed in relation to the following angiogenesis, cell cycle progression, hormone receptor activity, signal transduction and cell survival. This review will focus on the most recently published data, including experimental agents showing activity in endometrial cancer.

**Discussion**

**Bevacizumab**

Bevacizumab is the most widely studied antiangiogenic monoclonal antibody and is currently part of the standard treatment for advanced ovarian cancer, following two large Phase III randomised trials. In a Phase II trial in recurrent endometrial cancer, 56 patients were treated with bevacizumab 15 mg/kg until disease progression or unacceptable toxicity. The majority of patients had received at least one line of chemotherapy and half of them had radiotherapy. Median PFS and overall survival times were 4.2 and 10.5 months, respectively. Twenty-one patients were progression-free in 6 months. There was no clear association between response and particular histologic subtypes. The role of VEGF-A expression was investigated, concluding that high pre-treatment levels of circulating VEGF-A were correlated with poor outcome.

More recently in a Phase II setting, bevacizumab was combined with temsirolimus in recurrent endometrial cancer. A total of 53 patients received bevacizumab 10 mg/kg every 2 weeks and temsirolimus 25 mg IV weekly until the stage of disease progression or unacceptable toxicity. More than 80% of patients had received one line of chemotherapy. There were 12 clinical responses and 23 patients remained progression-free for 6 months. Complications were as expected, including two intestinal-vaginal fistulas, two GI perforations and a Grade 4 thromboembolism. Three deaths were potentially treatment related. Therefore, the combination seems active, but future studies will need to focus on safety issues.

The same combination of bevacizumab and temsirolimus has been investigated in combination with liposomal doxorubicin in a Phase I study. Among the 15 endometrial cancer patients who participated, there were 6 responses. Maximum tolerated doses were 30 mg/m² for doxorubicin and 15 mg/kg every 21 days for bevacizumab.

Ombrabulin, a vascular-disrupting agent derived from combretastatin A4-phosphate is another agent under investigation in combination with bevacizumab. It induces rapid tumour vascular shutdown via endothelial cell damage and resistance may occur by surges in circulating endothelial progenitors (CEP) that repopulate the tumour vasculature. Experimental models suggest prolonged and synergistic anti-tumour activity when ombrabulin is combined with VEGF-blockade, with reduction in CEP surge. A Phase I study evaluated the combination with bevacizumab in 39 heavily pre-treated patients. Ombrabulin was given in doses up to 50 mg/m² IV and bevacizumab up to 15 mg/kg every 21 days. There were no dose-limiting toxicities reported. Drug-related Grade 3 to 4 treatment adverse events were hypertension (6/39, 15%), intestinal perforation (2/39, 5%), headache (1/39, 3%), myocardial infarction.

Licensee OA Publishing London 2013. Creative Commons Attribution Licence (CC-BY)

**For citation purposes: Timotheadou E. Emerging targeted agents in endometrial cancer treatment. OA Cancer 2013 Jul 01;1(1):9.**

**Competing interests:** none declared. Conflict of interests: none declared. All authors contributed to the concept, design, and preparation of the manuscript, as well as read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
(1/39, 3%), and pulmonary embolism (1/39, 3%). There were two partial responses in ovarian cancer patients and another two CA125 responses in endometrial cancers, lasting more than 6 months\(^1\). Further evaluation of the drug is anticipated.

**Lenvatinib (E7080)**

Lenvatinib is an oral receptor tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT and PDGFR\(\beta\). In May 2013 it was granted orphan drug designation (ODD) for the treatment of radioiodine-refractory differentiated thyroid cancer (RRDTC) by the European Commission. Currently, there is an ongoing randomised Phase III study versus sorafenib in hepatocellular carcinoma and there are Phase II trials in melanoma and lung cancer. Also, there is an active Phase I/II study in advanced renal cell cancer in combination with everolimus (NCT01136733).

In endometrial cancer, the first results of a Phase II study have showed some activity and acceptable toxicity profile. The drug was given in 133 pre-treated patients with recurrent tumours at a standard dose of 24 mg PO once daily. Response rate as observed by the Independent Review Committee was 14.3%, median PFS was 5.4 months and median OS 10.6 months. Low baseline plasma level of Ang-2 (cut-off value $<2082$ pg/ml) was the only marker found to have a positive correlation with higher response rates, PFS and overall survival\(^1\).

**Dovitinib (TKI258)**

Dovitinib (DOV) is a potent receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor and FGFR. It is being studied as second-line treatment in advanced or metastatic endometrial cancer. Patient selection includes both mutated and wild-type fibroblast growth factor receptor-2 (FGFR2)\(^1\).\(^5\).

**CridanimoD**

CridanimoD is a novel small molecule that has been shown to increase progesterone receptor (PR) expression in rat endometrium. In a recently presented study it has been shown that combined progesterin and cridanimoD therapy can significantly improve survival of mice with high-grade, advanced endometrial cancer. CridanimoD significantly increased PR expression, and the concept of concurrent treatment with progesterins is being considered as a way to upregulate hormone receptors and achieve higher response rates in endometrial cancer. This effect is potentially mediated by cridanimoD-induced IFN-\(\alpha\) and \(\beta\) expression\(^1\). Based on these activity data, further investigation seems appropriate to assess the agent in a more advanced level.

**IMGN853**

IMGN853 is an antibody–drug conjugate (ADC) comprising a folate receptor 1 (FOLR1)-binding antibody and the potent maytansinoid DM4. Endometrial cancer among other solid tumours, frequently presents with FOLR1 overexpression and has been included in a Phase I study to test IMGN853 activity. The drug was given intravenously every 21 days with a dose escalation design. There was no significant toxicity observed, and there might be some activity in endometrial and ovarian cancer to be further investigated. The study is ongoing\(^1\).

**Linsitinib**

Linsitinib (OSI-906) is an oral dual inhibitor of insulin-like growth factor receptor-1 (IGF-1R) and insulin receptor (IR). Increased activity of IGF-1R and IR has been observed in solid tumours and is correlated with resistance to chemotherapy. The combination of linsitinib with weekly paclitaxel 80 mg/m\(^2\) in 21-day cycles was tested in a Phase I study. Linsitinib was given orally twice daily, either continuously or intermittently on Days 1 to 3 of each week. Fatigue, nausea, alopecia and diarrhoea were the most common toxicities observed. Among the 58 participating patients there were 6 responses and 25 cases with stable disease; each group included one patient with endometrial cancer. The Phase 2 part of the study is designed for ovarian cancer patients only and the results are pending\(^1\).

**MK-2206**

MK-2206 is an allosteric inhibitor of AKT, an effector kinase of PI3K signals. It inhibits proliferation of PI3K\(\alpha\)-driven cancer cell lines in vitro and causes regression of PIK3CA-mutant tumour models in vivo. PI3K pathway has been shown to have many alterations in endometrial cancer, including PTEN mutations (50%) or IHC loss (>50%), PIK3CA mutation (25%-40%) and PIK3R1 mutation (20%). Based on the hypothesis that PIK3CA mutation carriers are more likely to benefit from an AKT inhibitor, MK-2206 was tested in a Phase II study including 37 patients. Accrual was interrupted due to non-availability of mutation testing results before enrolment, but initial results revealed that MK-2206 has limited single-agent activity, both in mutant and wild-type PIK3CA\(^2\).

**BYL-719**

BYL719 is an oral small-molecule inhibitor of the p110\(\alpha\) catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which is encoded by the PIK3CA gene. It inhibits proliferation of PI3K\(\alpha\)-driven cancer cell lines in vitro and causes regression of PIK3CA-mutant tumour models in vivo. It has been tested in a Phase I study\(^3\) in 36 heavily pre-treated patients carrying a somatic mutation of PIK3CA, and among the seven responders, one had endometrial cancer. Dose-limiting toxicities were hyperglycaemia, nausea, vomiting and diarrhoea, and the maximum tolerated dose was 400 mg/d.

Licensee OA Publishing London 2013. Creative Commons Attribution Licence (CC-BY)

Conclusion
The need for more effective treatments in recurrent endometrial cancer offers significant motivation for testing new agents in therapeutic procedures. Identification of specific gene mutations or target molecules remains the focus for the ongoing research. There are promising data arising from the combination of approved drugs like bevacizumab with novel agents that are under investigation, and currently angiogenesis seems to be one of the more active areas of research in gynaecologic oncology in general and more specifically in endometrial cancer. Also, the study of specific signal transduction pathways like the PI3K pathway may open up new possibilities for targeted treatment, as more targets are identified and tested, both as single agents and in combinations and/or with chemotherapy.

A great challenge to be tackled in the future is the need to identify subgroups of patients sharing molecular characteristics that can make them eligible for a specific agent, so that only potential responders receive each drug, keeping in mind that the highest goal in development of new therapies is individualisation of treatment.

References