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Review

Endometrial cancer—targeted therapies myth or reality? Review of current targeted treatments

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Abstract Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries and its incidence is increasing related to obesity. EC is divided into histologic subtypes, most frequently endometrioid adenocarcinoma. Options for treatment of advanced or persistent disease remain limited, and survival has not changed in the last decade. No targeted therapy beyond hormonal therapy is approved for EC. Though hormonal therapy has been a 'standard' for four decades, prediction of its efficacy with receptor evaluation or understanding mechanisms of resistance remain important challenges. The clinical impact of deregulation of different pathways such as phosphatidylinositide 3-kinase, HER or MAPK warrant further investigation to use in a prognostic or predictive manner. The cell cycle and DNA repair pathways constitute potential targets for the development of precision therapies. Targeting the microenvironment and more recently immune infiltration are promising areas. Advances in the understanding of cell biology have allowed EC to be divided into multiple diseases that respond differently to targeted therapy. Translational clinical trials that link biology with precision targeted therapy are key to improve outcome and will require careful analysis or identification of potential biomarkers in early phase studies and validation in randomised trials. This approach requires collaborative efforts to achieve meaningful improvement in the prognosis of women with EC. This review aims to summarise the latest published trials on targeted therapies in EC and propose future directions.

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1. Biology: background for targeted therapy

In North America and Europe, endometrial cancer (EC) is the most common gynaecological cancer with expected 54,870 new cases and 10,170 deaths in 2015 compared to 49,560 and 8190, respectively, in 2013 in the United States alone [1,2]. This is a disease which is seen in older women, and more than 90% of cases occur in women over 50 years of age. Obesity is a well-described risk factor and has led to a worrying rise in the incidence of EC and it is likely to continue to increase.

1.1. Risk factors

Well-established risk factors for EC have been identified, and in some cases, these may inform and be of relevance for future development of therapeutic interventions. Long-lasting endogenous or exogenous hyper-oestrogenism, such as polycystic ovarian syndrome, tamoxifen therapy, anovulation, nulliparity, early age of menarche, and later age of menopause onset, are all associated with the development of EC [3–6]. In contrast, epidemiologic data show that the use of oral contraceptives confer long-term protection against endometrial cancer [7]. Type II diabetes and obesity (body mass index > 30) increase the risk of EC threefold to fourfold, and this is concerning as obesity has reached epidemic proportions globally. A recent study provides evidence to support a causal association of higher insulin levels, independent of body mass index, with endometrial cancer risk [8].

EC is also associated in approximately 5% of cases with inheritable germline mutations including loss of DNA mismatch repair as seen in Lynch syndrome [9]. Women diagnosed with the Lynch syndrome often present with EC as the first cancer-related diagnosis in 40–60% of patients. The Cowden syndrome, a rare autosomal dominant disorder caused by pathogenic mutations in the phosphatase and tensin homolog (PTEN), is known to be at risk of EC [10]. The identification of these women with inherited predisposition to EC is important for the patient in terms of potential targeted treatment and surveillance of associated cancer risk, and for the identification of at-risk family members who may benefit from appropriate screening and preventive strategies [11].

1.2. Histopathological features

Since 1983, EC has been classified in two subgroups based on clinicopathological characteristics. Type I or oestrogen-dependent endometrioid EC represents 70–80% of cases. This oestrogen-related pathway EC is associated with endometrial hyperplasia secondary to oestrogenic stimulation, most commonly low-grade, endometrioid differentiation, hormone receptor-positive endometrial cancer. Within type 1 EC, the phosphatidylinositide 3-kinases (PI3K)/protein serine–threonine kinase AKT pathway is the most frequently altered [12]. Type 2 EC consists of the oestrogen-independent non-endometrioid carcinoma such as serous, clear cell carcinoma, carcinosarcoma, mucinous adenocarcinoma, squamous cell carcinoma, and mixed adenocarcinoma [13]. This oestrogen-unrelated pathway EC arises from an atrophic endometrium. They are usually high-grade carcinomas of non-endometrioid differentiation, aneuploid, and negative/weak expression of hormone receptor. The most common molecular alterations observed are p53 and p16 mutations, HER2 overexpression or amplification and loss of E-cadherin. High-grade endometrioid EC does not fit into this dualistic classification [14].

1.3. Molecular characteristics

Recent integrated genomic characterisation of EC has identified four distinct molecular subgroups: (i) POLE ultramutated (catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair); (ii) microsatellite instability (MSI) hypermutated; (iii) copy number low and microsatellite stable; and (iv) copy number high serous like [12]. The POLE ultramutated subgroup is the smallest subpopulation characterised by POLE exonuclease domain mutations, ultra high somatic mutation load and excellent prognosis [15,16]; 60% of POLE ultramutated endometrial cancers are high-grade endometrioid lesions and 35% harbour TP53 mutations. The serous subgroup is characterised by high-grade TP53 and somatic copy number alterations that display genomic instability.

Uterine serous tumours and approximately 25% of high-grade endometrioid tumours have extensive copy number alterations, few DNA methylation changes, low oestrogen/progesterone receptor (PR) levels and frequent TP53 mutations [12]. As such, uterine serous carcinoma is a unique and biologically aggressive subtype of endometrial cancer and should be studied as a distinct entity [17]. MSI is more frequent in endometrioid than in non-endometrioid tumour and occurs in roughly 30% of sporadic cases of EC [12,18]. High-grade endometrioid EC are heterogeneous and can be also defined as ultramutated POLE.

One of the most pathway alterated in EC is the PI3K/AKT pathway; alteration described in 92% and 60% of type I and II tumours, respectively [12]. EC has more frequent mutations in the PI3K/AKT pathway than any other tumour type studied by The Cancer Genome Atlas. The PI3K/AKT/mammalian target of rapamycin (mTOR) signalling pathway regulates central aspects of cancer biology, such as metabolism, cellular growth, and survival [19]. Upon stimulation of receptor tyrosine kinases, PI3K phosphorylates phosphatidylinositol-4,5-bis-phosphate 2 (PIP2) into PIP3 resulting in the