Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU26856

Mechanisms and Emerging Targeted Therapies of Uterine Serous Carcinoma

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Abstract. Categorized as a subtype of endometrial cancer, uterine serous carcinoma (USC) is the most destructive among other subtypes, where surgery, chemotherapy, and radiotherapy were historically the only curative modalities. Although these modalities may appear significantly effective, the first 5-year survival rate after first-phase treatments remains low due to the high recurrence rate of USC tumors. To address these challenges, many tests are done to identify mutated genes, and corresponding targeted therapies are developed, such as TP53-targeting drugs, HER-2-targeted therapies, and immune checkpoint inhibitors (ICIs), which will be elaborated on in the subsequent sections. The main reason for developing targeted therapies is that the side effects are significantly reduced compared to conventional therapies; they offer greater precision, which leads to better outcomes, and a possible cancer-free future for patients. This paper provides an overview of mechanisms and emerging targeted therapies for USC, along with a brief analysis of USC and its conventional therapies, which offers new ideas and directions for pathological research and clinical treatment of USC and other complex cancers.

Keywords: Uterine Serous Carcinoma, targeted therapies, TP53, HER2, ICIs.

1. Introduction

Identified as an aggressive subtype among other branches of endometrial cancer, USC is classified as endometrial cell carcinoma. Most USCs are detected and diagnosed during menopause due to abnormal bleeding, but a subset of cases arises prior to menopause [1]. USC constitutes a small fraction of all identified endometrial cancers, approximately 10%, but it accounts for around 40% of endometrial-related deaths. Patients treated in the early stage have a 5-year overall survival rate of only 10%-20% [2]. There are conventional methods such as surgery, chemotherapy, and radiotherapy that aim to reduce the spread of cancer to other organs and promote tumor regression. Despite all these efforts, the recurrence rate is still high, accompanied by severe side effects including fatigue, dizziness, nausea, and an elevated risk of infection due to low white blood cell counts. Recent studies have focused on identifying targeted therapeutic approaches for USC. It is generally believed that the malignancy observed in USC is primarily driven by the following mutations: TP53, HER2, PPP2T1A, FBXW7, and CCNE1 amplification. The emerging therapies described in this paper include TP53-targeting drugs, HER-2 targeted therapies, and immune checkpoint inhibitors (ICIs). Several drugs classified as antibody-drug conjugates (ADCs) will be

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mentioned, along with their clinical trial results that demonstrate their effectiveness. In recent years, uterine serous carcinoma (USC) treatment has undergone a major shift from general chemotherapy to biomarker-driven targeted therapies, such as TP53-targeted therapies, HER-2-targeted agents, and the use of antibody-drug conjugates (ADCs). Employing such strategies significantly improves survival rates among USC patients, which marks a major step forward in curing lethal diseases.

2. The pathological mechanisms of USC and conventional treatment methods

USC is a lethal cancer type that has low survival rates and a high recurrence rate compared to other categories of cancer. Specifically, USC is classified as a deviation or subtype of endometrial cancer. However, it constitutes a minor portion of the overall number of patients who have endometrial cancer; yet it results in the highest mortality rate [2]. Numerous factors elevate the risk of developing USC, such as a medical history of breast cancer, genetic heredity, and TP53 or other gene mutations. The reason that breast cancer escalates the likelihood of developing USC is that the use of tamoxifen is a primary contributing factor in breast cancer treatment. Research data show that 31% of women with breast cancer develop USC, compared to 18% of those without breast cancer [3]. At the time of USC diagnosis, mutations in TP53, HER2, FBXW7, and PPP2R1A are often observed, accompanied by amplification of CCNE1 and MYC. These are key genes involved in tumor suppression or oncogenesis.

Before targeted drugs were developed, conventional therapies are applied to patients with cancer. These methods are surgery, chemotherapy, and radiotherapy. Surgery directly removes the tumor from the body. While this approach may seem highly effective, it has limitations: a high rate of metastasis, i.e., the spread of tumors to other organs; a high recurrence rate, especially at the peritoneum and omentum, where recurrence can reach as high as 31% at the peritoneum and 17% at the omentum; and the risk of infection after surgery. Although the procedure itself is not complex, many patients are over 65 years old, making surgery a significant burden on their immune systems [4]. Despite these risks, surgery offers a valuable chance for patients to achieve remission, as the tumor needs time to grow back to its original size. Chemotherapy uses drugs that disrupt the normal cell cycle, since cancer cells proliferate by mutating certain genes during the DNA replication process and/or altering components responsible for checking mutation errors, such as DNA polymerase II, which proofreads newly synthesized DNA. Some drugs achieve this effect, such as paclitaxel. Paclitaxel prevents microtubule depolymerization, thereby preventing cells from progressing from metaphase to anaphase. Radiotherapy uses beams of energy to kill tumor cells. Image-Guided Radiotherapy (IGRT) is used to produce precise images of where charged particles should be delivered. When high-energy beams reach cancerous tissues, they kill the cells, resulting in control of tumor growth or even tumor regression. Additionally, this therapy is compatible with other therapies such as chemotherapy to achieve optimal tumor regression [5]. The conventional therapies described above have severe side effects, such as nausea, lowered immune response, and a high risk of infection, which can be fatal, and they rarely ensure patients remain cancer-free after treatment. Therefore, the development of targeted therapies with fewer side effects is crucial.

3. Emerging therapies

3.1. TP53 targeting therapies

TP53 is a vital tumor suppressor in healthy cells that encodes the p53 protein. Key functions regulated by p53 include apoptosis, DNA repair, and cell cycle halt. Apoptosis is triggered when

DOI: 10.54254/2753-8818/2025.AU26856

damage is considered irreparable. When this function is altered due to mutation, it can bring severe consequences, such as malignant proliferation of cells, a commonly seen feature among USC patients, as the cellular "brake" is defective, allowing unchecked replication. Although this may seem like an easy target for drugs, the intracellular mutations in p53 make it difficult to target directly. Unlike HER2 mutations, in which mutated proteins are on the cell surface, the p53 protein mutation is in the cell near the nucleus, where antibodies and drugs cannot reach directly. TP53 mutations are commonly seen in the DNA-binding section, which is related to transcription functions [2]. One approach to address this problem is to restore the function of p53 by using a drug called PC14586. The p53 mutation is caused by the mutant p53 Y220C protein, which distorts the shape of the original protein, causing it to lose its original function. Specifically, PC14586 can restore p53's function because mutant p53 Y220C has a crevice where PC14586 can bind. Due to this characteristic of mutant p53 Y220C, PC14586 can restore the protein's original function and conformation. One example of a p53-targeting drug is bevacizumab. A study demonstrated its effectiveness in the GOG-86P phase 2 trial, where patients received multiple drugs that were assumed to be effective. Bevacizumab performed better than other drugs, as evidenced by a cancer-free period of 12.5 months compared to 8.2 months for other drugs [2].

3.2. HER-2 targeted therapies

Human epidermal growth factor receptor 2, or HER2 for short, is also called ErbB2 and functions as a transmembrane tyrosine kinase receptor. In particular, HER2 is a kind of protein that is usually found on the cell surface as a member of the HER (ErbB) family of receptor tyrosine kinases. HER2 is a receptor that conducts biochemical signals by dimerization in the plasma membrane. In USC patients, HER2 is overexpressed and ErbB2 is amplified. Typically, overexpressed HER2 functions as an oncogene, causing tumor cells to proliferate at a rapid rate. Normal cells have two copies of HER2, but in the case of overexpressed HER2, there are up to 100 copies per tumor cell. The mechanism underlying this uncontrollable cell proliferation in USC is that an excess of HER2 receptors can undergo heterodimerization or homodimerization, and overexpression of HER2 leads to increased autophosphorylation, creating sites for signaling molecules such as PDGF and EGF to bind. More importantly, this autophosphorylation occurs without a ligand, so the signaling is always on. This characteristic of mutated HER2 genes often leads to a high recurrence rate, spread of tumors, and reduced survival rate. Using a technique called immunohistochemistry (IHC), the malignant proliferation of cells is detected and further confirmed with fluorescence in situ hybridization (FISH) [2]. Given that HER2 and ERBB2 are prominent features identified in these tests, targeted drugs have been developed to target them. These drugs are often classified as antibody-drug conjugates (ADCs), one example is trastuzumab, a humanized monoclonal antibody used to treat HER2-positive patients, which binds specifically to HER2. The effect of trastuzumab on HER2 can be evaluated from two perspectives: (1) ligand-independent heterodimerization of HER2, and (2) ligand-dependent heterodimerization and homodimerization. According to results using a reversible cross-linker, ligand-independent heterodimerization formation is disrupted by trastuzumab, but the heterodimers remain unaffected. For ligand-dependent heterodimerization and homodimerization, trastuzumab inhibits homodimerization by binding to the receptors on HER2. This is why trastuzumab is considered a success in targeting HER2 receptors. However, this drug has limitations. Some studies indicate that trastuzumab is not effective in suppressing HER2 heterodimerization in breast cancer cell lines, and it is less effective when used as a single agent in later stages of endometrial cancers [6, 7]. Trastuzumab is recommended to be combined with other therapies to maximize its effectiveness [6]. This drug is categorized as an ADC because it meets the

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criteria of consisting of an antibody and a linker. Moreover, the abundant HER2 present on the cell surface makes it a good target for drugs [8].

3.3. Immune checkpoint inhibitors therapies

Immune checkpoint inhibitors utilize the body's immune system to target tumors, specifically by modifying T cells. Cells have checkpoints on their surface to prevent the immune system from being overactive and attacking normal tissues. Checkpoints that have demonstrated notable success in treating patients with cancer are PD-1, PD-L1, and CTLA-4 [9]. On the majority of activated immune cells, PD-1 is commonly expressed on their surface. For example, B cells, T cells, and dendritic cells all match this pattern. Among all of these, PD-1 is expressed primarily on exhausted T cells. It is responsible for regulating programmed cell death. The mechanism by which PD-1 regulates cell proliferation is through phosphorylation of the immunoreceptor tyrosine-based switch motif (ITSM). It then enlists SRC homology region 2 domain-containing phosphatase-2 (SHP-2), which is primarily responsible for repressing the activity of molecules that regulate the proliferation signals of T cell receptors (TCRs) [10]. One such inhibitor is nivolumab. This drug can be applied not only to USC patients, but also to patients with NSCLC, urothelial cancers, and other conditions. Clinical trial data demonstrate that nivolumab yields better outcomes than docetaxel. Specifically, nivolumab exhibits a median survival of 9.2 months compared to docetaxel's 6 months [11]. PD-L1 is a ligand protein often found on tumor cells. As a ligand present on most tumor cells, PD-L1 interacts with itself on cytotoxic T cells, resulting in amplified tumor growth. Thus, administration of the antibody, anti-PD-L1, will result in a stagnation of malignant cell growth. In a clinical trial where patients were given an anti-PD-L1 antibody, pembrolizumab, the patients exhibited full or limited feedback to the drug, proving its effectiveness. In the following clinical trial, over 30% of the patients with progressive stages of cancer responded to pembrolizumab, compared to 12% of patients administered ipilimumab [10]. The last common checkpoint in ICI is CTLA-4, which is a repressive receptor commonly seen on T cells. The mechanism by which CTLA-4 releases inhibitory signals to induce T cell deactivation is that T cells require two stimulations to become activated, and this is where CTLA-4 comes in. First, when T cells encounter their cognate antigen, the stimulation of the TCR and the interaction between CD28 on the T cells and antigen-presenting cells (APCs) that exhibit CD80 or CD86 will occur. When TCR signals are induced, CTLA-4 molecules originally stored inside the cell will move towards the cell surface, competing to bind CD28 ligands that activate T cells. Once more CTLA-4 molecules bind to CD28 ligands, T cell activity is inhibited. The process described above demonstrates the extrinsic mechanism of how CTLA-4 constrains T cell activity. The intrinsic mechanism of how CTLA-4 obstructs T cells involves recruiting the phosphates lost during activation via signaling the receptors and inhibiting proteins that code for transcription, such as NFAT [10]. The combination of ipilimumab with nivolumab can achieve a better response rate of 36%, which is significantly better than the 28% response rate with single-agent therapy. Additionally, the disease control rate is at 58% [12].

4. Conclusion

This review lists three main emerging therapies with significant potential for treating USC patients in the future: TP53, HER2 targeting therapies, and ICIs. The mechanism of each therapy is explained, and some differences between HER2 and TP53-targeting therapies are also noted. Specifically, TP53 involves an intracellular mutation in the DNA-binding domain, affecting transcription-related functions. Since the mutation is within the cell, antibodies cannot directly reach

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it, thus making it harder for drugs to target. However, HER2 targeting is easier than TP53 because the overexpressed proteins are on the surface of the cell, where they come into direct contact with drugs. Targeted therapies for HER2 mainly disrupt heterodimerization and homodimerization of ligands; the drug trastuzumab achieves this goal as evidenced by data from clinical trials. For immune checkpoint inhibitors, this is an approach that utilizes the immune system in the body to achieve stagnant tumor growth or tumor regression. Specifically, there are three checkpoints commonly used: PD-1, PD-L1, and CTLA-4. Each is responsible for regulating programmed cell death by either inhibiting molecules that code for proliferation or activation of T cells. Each therapy's mechanism is also explained briefly to provide an overview of how each drug functions. Finally, different aspects that need careful consideration when developing targeted drugs are discussed in the ADC section. After explaining both the traditional and newly developed therapies, a future direction might be combining these therapies based on each patient's conditions to achieve the best effect of each treatment method. These research advances have injected new vitality into the precision development of cancer treatment and opened up broader prospects for overcoming the challenges of complex cancers.

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