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INNOVATIONS IN CERVICAL CANCER THERAPY: THE IMPACT OF IMMUNOTHERAPY ON HEALTH SYSTEMS AND EDUCATION

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ABSTRACT

Cervical cancer is one of the most common genital malignancies in women worldwide, although its development is largely preventable through effective primary and secondary prevention programs. The main cause of the development of this cancer is chronic infection with oncogenic types of human papillomavirus (HPV), particularly types 16 and 18. The introduction of HPV vaccination and regular screening (cytology, HPV DNA testing) has significantly contributed to the decline in incidence in developed countries. Unfortunately, in many regions of the world, including Poland, vaccination and screening rates remain inadequate, resulting in a high incidence and death rate. The standard treatment for locally advanced cervical cancer is combination chemoradiotherapy, which combines radiotherapy with the simultaneous administration of cisplatin. In recurrent and metastatic cases, where radical treatment is not possible, systemic treatment is used - mainly chemotherapy based on a combination of cisplatin and paclitaxel, often with the addition of bevacizumab, an angiogenesis inhibitor. Advances in targeted therapies and immunotherapies (e.g., PD-1/PD-L1 checkpoint inhibitors) are opening up new therapeutic options, increasing the chances of prolonging survival and improving quality of life for patients with advanced disease. Numerous clinical trials are currently underway to evaluate the efficacy of new drugs and combination treatment strategies. There is also a growing emphasis on personalizing therapy based on molecular biomarkers. Effective control of cervical cancer requires an integrated approach - combining prevention, early detection, and access to modern treatments. The future of the fight against this cancer involves global implementation of HPV vaccination, expansion of screening programs, and development of precision systemic therapies. This review synthesizes the current state of knowledge, challenges, and new directions in the prevention, diagnosis, and treatment of cervical cancer.

KEYWORDS

Cervical Cancer, Human Papillomavirus (HPV), Tumor Microenvironment, Checkpoint Inhibitors, Adoptive T Cell Therapy, Pembrolizumab, Cemiplimab

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Introduction.

Cervical cancer represents one of the most serious oncological challenges globally, being the fourth most common cancer in women and one of the leading causes of cancer deaths, just after breast, colorectal, and lung cancer [1,2,3]. According to the World Health Organization in 2020, the number of new cases was about 604,000, and the number of deaths reached 342,000 [2,4]. Cancers dependent on human papillomavirus (HPV) infection, such as cervical, anal and oropharyngeal cancers, develop in organs with high exposure to the pathogen. HPV is responsible for nearly 90% of cervical and anal cancers, and up to 30% of cancers in the oral cavity, vagina, vulva and penis [5]. The predominant histopathological type of cervical cancer is squamous cell carcinoma (about 80%), but in recent decades, there has been an increase in the incidence of adenocarcinoma [3]. Chronic infection with high-risk HPV, particularly types 16 and 18, remains the most important etiologic factor, as officially recognized by the WHO and other scientific institutions, such as the European Organization for Genital Infection and Cancer Research [4]. However, other risk factors, such as early initiation of intercourse, multiple sexual partners, lack of condom use, multiple pregnancies, and infection with other pathogens - including HIV and chlamydia - also influence the development of the disease [4,5]. HPV infection is usually asymptomatic. Asexual warts, which appear as flat, papular, or cauliflower-like growths, are usually diagnosed by clinical examination. Recurrent respiratory papillomatosis, a rare condition, usually presents with hoarseness and stridor and requires referral to an otolaryngologist. Most genital HPV infections are diagnosed by HPV testing as part of cervical cancer screening [6]. Although the introduction of HPV vaccination has significantly reduced the incidence of infection with the most oncogenic strains of the virus, there is still a high incidence and death rate from cervical cancer, especially in countries with limited access to health care [4,7]. Primary prevention (vaccination) and secondary prevention (screening, such as cervical cytology) are particularly effective in reducing the incidence of this disease, as the experience of developed countries confirms. However, many developing countries with fewer health care resources still have the highest rates of cervical cancer incidence and mortality [7]. Cervical cancer is a cancer that, with the right approach, can be successfully treated, especially if detected at an early stage [4]. Unfortunately, in practice, most cases are diagnosed at more advanced stages of the disease - only 13% of patients receive a stage I diagnosis. In comparison, as many as 44% receive a stage III diagnosis [8]. With late detection, the chance of survival decreases - the five-year survival rate for locally confined cancer reaches 91.5%, while it drops to 16.5% for metastatic cancer [4]. The treatment regimen for cervical cancer depends on stage and is based on the FIGO and TNM classifications. Available treatment options include surgery, radiation therapy, chemotherapy, and systemic therapies, including immunotherapy and targeted drugs. Since 1999, concurrent chemoradiotherapy has remained the standard treatment for locally advanced forms of the disease (stage IIb-IVa) [7]. For patients with recurrent or metastatic cervical cancer (stage IVb), a combination of cisplatin, paclitaxel, and bevacizumab is used, yielding a 48% response rate and a median survival of 17 months [7]. In recent years, interest in the use of immunotherapy to treat HPV-dependent cancers has increased significantly. The high mutational burden of the tumor (TMB), the presence of viral antigens, and the infiltration of CD8+ lymphocytes make cervical cancer a suitable candidate for immunomodulatory therapies [5,7]. Although therapies such as therapeutic vaccines and adoptive cell therapy (ACT) have provided limited benefit, checkpoint inhibitors, such as pembrolizumab, have significantly expanded therapeutic options. Today, these drugs are already approved for the treatment of advanced forms of cervical cancer in many countries [7].

Materials and Methods

A comprehensive review of articles published in scientific journals was conducted using online research platforms such as PubMed and Google Scholar. Articles were identified using the following search terms: "Cervical cancer", "Human papillomavirus (HPV) „Squamous cell carcinoma", „Cervical intraepithelial neoplasia (CIN)", „Tumor microenvironment", „Immunotherapy", „Checkpoint inhibitors", „Adoptive T cell therapy".

Discussion

Epidemiology

According to the World Health Organization (WHO), each year, more than 600,000 women worldwide receive a diagnosis of cervical cancer [9]. The highest burden of the disease is observed in regions with limited financial, educational, and medical resources, where the highest incidence rates occur. It is estimated that as many as 84% of all cases and 88% of deaths from this cancer occur in countries with low levels of social development [1]. Particularly high incidence and mortality rates are recorded in Africa, Melanesia, South America, and regions of Southeast and Central Asia [10,11]. In sub-Saharan Africa, which is also the area most

affected by the HIV pandemic, cervical cancer remains the leading cause of oncological mortality among women [12]. In countries with high HDI levels, the five-year survival rate for patients with this cancer is 60 to 70%, while in countries with low HDI, it falls below 20% [2]. This dramatic disparity is mainly due to limited access to preventive programs, such as HPV vaccination and early diagnosis of precancerous lesions through screening [13]. In regions where adequate screening systems are lacking, cancer is usually detected only at the invasive stage [1]. The average age of cervical cancer diagnosis is now 55, but about a quarter of cases are in women younger than 35 [3].

In response to the growing problem, the WHO has initiated a global strategy to eliminate cervical cancer, based on three pillars: universal HPV vaccination, effective screening programs, and access to treatment [1,2]. It is projected that implementation of this approach in low- and middle-income countries could reduce cervical cancer mortality by up to 88.9% over the next five decades [1,3].

Risk factors

Cervical cancer, like many other malignancies, develops as a result of a complex interaction of genetic and environmental factors [14]. Although classic oncologic risk factors such as cigarette smoking, long-term use of hormonal contraceptives, low socioeconomic status or a weakened immune system (e.g., as a result of HIV infection or use of immunosuppressive drugs after transplantation) contribute to the development of the disease, a key etiologic role is attributed to human papillomavirus (HPV) infection [3]. Differences between HPV variants have attracted increasing attention in the context of cervical carcinogenesis. These variants are characterized by different biological and pathological properties, which may affect their ability to cause neoplastic lesions [15]. In the initial stages of high-risk virus (hrHPV) infection, the disease develops asymptomatically. In the absence of early detection, neoplastic transformation can occur, resulting in precancerous lesions and then invasive cervical cancer [10]. Some studies have suggested that other sexually transmitted viruses may act as additional drivers of cancer. For example, it has been suggested that the presence of herpes simplex virus type 2 (HSV-2) may play an important role in initiating cancerous processes within the cervix [15]. HPV is considered a necessary but not sufficient factor in the development of cervical cancer. The occurrence of full-blown cancer depends on the presence of multiple coexisting risk factors that interact with oncogenic HPV types in the process of cellular transformation [13]. Cellular immunity plays a key role in the immune response to HPV infection, so any disruption of this immunity, such as in the course of HIV or after transplants, significantly increases the risk of both infection and its progression [14]. In addition, the presence of HPV in one body location is associated with a significantly increased likelihood of its occurrence in other anatomical areas. According to studies, HPV infection in the rectum is a strong predictor of the presence of HPV infection in the cervix, and conversely, cervical infection may indicate HPV infection in the rectum [16].

Human papillomavirus

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted infections, affecting both men and women worldwide. Genital HPV infection is not notifiable, leaving accurate data on its prevalence unknown. Nevertheless, it is estimated that there are 1-5.5 million new infections each year, and the total number of infected people may be around 20 million [15]. Persistent HPV infection is a major factor leading to the development of malignancies of the cervix, but also of other anatomical areas such as the vulva, vagina, penis, anus, oral cavity, throat and head and neck region [3,12]. Of the more than 200 types of HPV, about 40 infect the reproductive system, 13 of which are considered oncogenic, or cancer-causing. This group includes types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 [12]. HPV types are classified into low-risk and high-risk, depending on their carcinogenic potential. Low-noncogenic types usually do not cause serious symptoms or lead to mild lesions such as condylomata. High-risk types, on the other hand, can lead to malignant transformation [17]. HPV infects basal epithelial cells - either cutaneous or mucosal - depending on the tropism of the strain. Cutaneous strains affect hands and feet, while mucosal strains colonize the membranes lining the mouth, throat, respiratory tract, and genital area [10,15]. An example of a benign but clinically significant HPV infection is focal proliferation of the oral epithelium (Heck's disease), usually caused by HPV-13 [15]. HPV genetic material includes both early (E1-E7) and late (L1 and L2) genes. The E1 and E2 genes are responsible for viral replication, with E2 also regulating the expression of the oncogenic genes E6 and E7. In turn, the E4 and E5 proteins promote viral replication and growth, while the capsid proteins L1 and L2 build the viral envelope [4]. Based on the sequences of the L1, L2 genes, and the LCR control region, five major HPV-16 clusters have been identified: European (E), Asian (As), Asian-American (AA), African-

1 (Af1), and African-2 (Af2). The oncogenic potential of these variants can vary depending on the geographic region and ethnicity of the population. For example, Asian-American isotopes may exhibit higher oncogenicity than European variants due to increased transcriptional activity and changes in response to progesterone [15,18]. It is now believed that more than 90% of cervical cancer cases are due to HPV infection, with more than 70% caused by types 16 and 18 [12]. In sexually active women, the rate of HPV infection is as high as 80% [1], but only 5-10% of the infections persist, and cancer develops in about 3% of cases [3]. HPV infections most often occur in the first few years after the onset of sexual activity, with most infections occurring between the ages of 15-25. It is estimated that 80% of oncogenic HPV infections occur before the age of 27 [19]. The transition process from HPV infection to developed cervical cancer takes an average of about two decades [3]. Persistence and progression of infection are strongly related to HPV type and immune status. In immunocompromised women, such as those with HIV, AIDS, or after transplants, the risk of developing cancer increases significantly. In addition, other risk factors include pregnancy history, use of oral contraception, smoking, chlamydia infection, obesity, and mental illness, among others [12]. Women infected with HPV have also been observed to have an increased risk of developing cancers in extra-cervical locations - including the rectum, vagina, vulva, throat, oral cavity, lungs and bladder - confirming the need for screening in these areas in at-risk individuals as well [16]. HPV is detected in almost all cases of cervical squamous cell carcinoma (99.7%). In the case of adenocarcinoma, the relationship is less clear and is age-dependent - in women under 40, the virus is present in 89% of cases, and in women over 60, only 43% [15].

Pre-cancerous states

The process of cervical cancer development involves several key stages, among which the most important are: initial HPV infection, persistence of infection, progression to dysplastic lesions, and further progression to the invasive stage. Importantly, this course is not irreversible – in many cases, the virus can be eliminated from the body, and precancerous lesions can regress [11,17]. Phenomena such as spontaneous clearance of infection or regression of dysplasia are relatively common, so most HPV infections are transient and do not lead to cancer. It is estimated that about 67% of HPV infections are spontaneously cured within a year of infection, without the need for medical intervention [17]. The development of cervical cancer usually occurs through progressive changes in the cervical epithelium, referred to as CIN (Cervical Intraepithelial Neoplasia) grades I to III. These lesions are also classified as low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and adenocarcinoma in situ (ACIS) [3]. The transformation of HPV infection into pre-cancerous lesions usually occurs within 5-10 years, with the highest incidence between the ages of 25 and 35. Without the implementation of treatment, about 30% of HSIL cases can progress to invasive cancer over time [19]. Modern clinical guidelines recommend that for CIN1 lesions, the patient's condition should be observed and monitored, without immediate surgical intervention. On the other hand, for more advanced lesions – CIN2 and CIN3 – various therapeutic methods are used, such as cryotherapy, thermal ablation, loop electrosurgical excision (LEEP) or conization with a surgical knife (CKC) [17].

Carcinogenesis

The life cycle of HPV begins by interacting with host cells, especially keratinocytes. The virus takes advantage of the microinjuries that occur, for example, during sexual contact, to attach itself to the cells and begin the process of multiplication and transcription of its genetic material. The early expression region of the virus (designated E) encodes several proteins, such as E1, E2, E1^E4, E5, E6, E7, and E8^E2, which have various functions during the replication cycle. Of particular importance are oncoproteins E6 and E7, which play a key role in inducing tumorigenic changes in host cells [16]. HPV-induced cell transformation relies mainly on the activity of these two proteins, which interfere with the mechanisms controlling cell growth and division. For the virus infection to progress, HPV must invade keratinocytes of the basal layer of the epidermis, which can divide. After entering these cells, the virus activates the early promoter, which initiates the production of genes needed for viral multiplication. The first proteins synthesized are E1 and E2, which are necessary to initiate replication of HPV genetic material [3]. The integration of HPV DNA into the host cell genome is an important step in the carcinogenesis of cervical cancer. Unlike transient infections, where viral DNA remains in an episomal form, persistent infection often leads to integration of the viral genetic material into the host DNA, raising the risk of highly malignant lesions and malignant transformation. A key effect of integration is the disruption of E2 gene function, resulting in deregulated expression of the E6 and E7 oncogenes. Overproduction of these proteins inactivates p53 proteins and the pRb family, which in turn leads to inhibition of controlled apoptosis, unrestricted cell proliferation, and cancer growth. In addition, integration

facilitates the virus's escape from the immune system by downregulating the expression of viral antigens and modulating immune responses, allowing infected cells to evade detection by the immune system. Oncoproteins E6 and E7 also inhibit the host's natural antiviral mechanisms [3,12,16]. An in-depth understanding of the mechanisms by which HPV evades the immune response is critical. The virus uses numerous strategies to evade recognition by immune cells, including interfering with detection processes and inhibiting inflammatory responses. HPV also manipulates immune receptors and affects the production of cytokines, which promotes the maintenance of infection and the development of cancer. This complex interaction between the viral genome and the body's defense mechanisms is important for both the development of cervical cancer and potential treatments [16].

Screening

Unequal access to screening is a major reason for the significant differences in cervical cancer incidence and mortality between countries with different levels of development. Screening programs aim to detect asymptomatic precancerous lesions in women, allowing early diagnosis and treatment, preventing the development of full-blown cancer [23]. Effective screening should be characterized by high sensitivity, reproducibility, and simplicity of performance, allowing it to be performed also by primary care physicians. For many years, cytology (Pap test) was the mainstay of such testing, but with a better understanding of the role of HPV in the etiology of cervical cancer, HPV testing has become more important [24]. Cytological testing involves a physician taking a sample of cells from the cervix during a speculum examination. These samples can be fixed traditionally on a slide or placed in a special liquid and then analyzed microscopically. The result may show normal cells, low-grade lesions (e.g., ASC-US, LSIL) that suggest HPV infection but do not immediately provide a diagnosis of premalignant lesions, or high-grade lesions (HSIL, atypical cells), which are often associated with more serious changes and require treatment to prevent invasive cancer. Cytology has a high specificity - detection of high-grade lesions is a strong indicator of the presence of precancerous conditions [19]. Reporting of cytology results has evolved, and the Bethesda system, which was introduced in 1988 and subsequently updated, is now widely used, replacing older classification systems [10,15]. Cytology-based programs have significantly reduced the incidence and mortality of cervical cancer in developed countries, where regular screening is standard. As a result, a decrease in incidence and death by more than 70% has been recorded in these countries [17]. Screening based on HPV detection involves the collection of material from the cervix or vagina to identify oncogenic types of the virus. The HPV test has a high sensitivity, detecting about 90% of precancerous lesions and cancers. Performing the test every 5 years is associated with a lower risk of cancer and precancerous lesions compared to cytology performed every 3 years [14]. In addition, HPV testing identifies cases of adenocarcinoma and its precursors better than cytology. The inclusion of HPV testing in screening programs leads to earlier detection of both squamous and adenocarcinomas, resulting in a reduction in cancer incidence within 5 years and mortality within 8 years [12,19]. Colposcopy is the classic diagnostic method used after abnormalities are detected by screening. During this examination, the cervix is viewed after application of acetic acid solution (3-5%), which causes discoloration of altered cells - dysplastic and HPV-infected cells reflect light and appear white. Lugol's iodine can also be used, which stains healthy cells rich in glycogen brown, while precancerous and cancerous cells, containing less glycogen, remain unstained [1,17]. International guidelines recommend screening women between the ages of 25 and 65 at a frequency that depends on the method used - for example, cytology every three years or HPV testing every five years. A combination of both methods, or combined testing, improves diagnostic efficiency and allows earlier detection of lesions, resulting in better treatment outcomes [25].

Human papillomavirus vaccination

Vaccination against human papillomavirus (HPV) is a key element in the global prevention of HPV infection, significantly reducing the risk of developing HPV-associated cancers [16]. In 2007, the Standing Committee on Immunization Practices (STIKO) introduced recommendations for prophylactic HPV vaccination, which initially included girls aged 9 to 14 years and, as of 2018, also included boys in the same age group. The protective effects of HPV vaccines against diseases of the anal area have also been shown in adult women and men between the ages of 14 and 45. In the United States, the Centers for Disease Control and Prevention (CDC) recommends starting vaccination routinely at age 11 or 12, with earlier doses as early as age 9, as well as booster doses until age 26 and optional vaccination for adults between ages 27 and 45 [3]. Currently, there are three FDA-approved HPV vaccines available on the US market: Gardasil, Gardasil 9, and Cervarix [17]. The Cervarix® vaccine, approved by the FDA in 2009, is a bivalent formulation that protects

against the two most common HPV types, 16 and 18, responsible for about 70% of cervical cancer cases. Studies show that the protection provided by Cervarix can last up to 10 years. Gardasil® is a quadrivalent vaccine targeting HPV-6, 11, 16, and 18, which are responsible for most genital warts and cervical cancers. In addition, Gardasil has shown efficacy in preventing HPV infections in other locations, such as the oral cavity, penis, vulva and anus. Gardasil 9® is an expanded version of this vaccine that protects against nine HPV types, including also 31, 33, 45, 53, and 58, preventing about 90% of cervical cancer cases [16,24]. Vaccination can reduce up to 70% of HPV-related cervical cancers and up to 90% of genital warts [3]. Recent data indicate that protection against the virus persists for at least 10 years for Gardasil, 9 years for Cervarix, and about 6 years for Gardasil 9 [17]. What's more, HPV vaccination also has a role in tertiary prevention - after surgical procedures in patients with cervical dysplasia (CIN I-III), a significant reduction in the risk of recurrent lesions has been shown, by as much as 58.7% [3]. Despite vaccination, regular screening for cervical cancer is still recommended, regardless of patients' vaccination history [6].

Treatment

Therapeutic decision-making in the treatment of cervical cancer requires the collaboration of a team of specialists that includes gynecologic oncologists, radiation oncologists, radiologists, and pathologists. An important aspect is to assess whether preserving the ability to procreate is desirable and possible [3]. Given that approximately 40% of women with cervical cancer are of childbearing age, issues of fertility preservation become crucial [4]. The decision-making process should take into account the patient's preferences, general health, risk factors, stage of menopause, and individual life circumstances [3]. Treatment is also selected based on such parameters as tumor size, stage, histologic features, presence of lymph node metastases, and risk of complications from surgery or radiation therapy [15]. Patients with stage IA1 cancer without the presence of risk factors can be treated by cervical conization and curettage or simple hysterectomy, especially if the margins after conization are positive, the family plan has been completed, or the patient prefers greater safety [3,15]. If there is a desire to preserve fertility and positive margins after conization, re-conization or trachelectomy with permanent removal of part of the cervix is an option [3,15]. For patients with stage IB1 cancer with a tumor diameter of less than 2 cm and no risk factors, radical hysterectomy is recommended, but when the patient wishes to preserve fertility, radical trachelectomy can be considered. In contrast, treatment of stage IIA1 cancer usually includes radical hysterectomy [3]. For locally advanced cancers, the standard treatment is radiation therapy [15]. In the treatment of advanced cervical cancer, a combination of chemotherapy based on platinum drugs and radiation therapy is used [10]. Cisplatin, which is the most commonly used agent in therapy, works by inducing cell apoptosis, causing DNA damage, and stopping the division of cancer cells [9]. Evaluation of lymph node status is one of the most important prognostic factors, and the determination of stage and prognosis is based on, among other things, intraoperative sentinel node (SNB) examination [4]. Sentinel node biopsy, recommended for early-stage cervical cancer (pT1a1 L1/pTIA 2 and pTIB1 $\leq$ 2 cm), is performed using technetium-99 and blue dye or a newer method using indocyanine fluorescence [3]. Despite treatment with concurrent chemotherapy and radiotherapy, more than half of patients with locally advanced cervical cancer experience recurrence or distant metastasis, indicating the need for further research to improve therapy. Currently, combinations of chemotherapy with immunotherapy, targeted therapies, and other modern treatments are being investigated [1].

Immunotherapy

Standard treatments, such as systemic chemotherapy, surgery, and radiation therapy, offer limited therapeutic options. Patients undergoing these therapies often experience significant pain and little improvement in survival rates [14]. In situations of chronic, recurrent, and metastatic disease, there has been a great need to seek more effective treatments [13]. Modern oncology has recognized immunotherapy as a breakthrough strategy that offers hope for controlling tumor growth and, in some cases, even a complete cure [12]. Immunotherapy for cervical cancer includes therapeutic vaccines, immune checkpoint inhibitors (ICIs), and T-cell-based therapies. Therapeutic vaccines have shown some efficacy in clinical trials for pre-invasive cancers, but their effectiveness in advanced cancers remains limited [9]. Immune checkpoints represent key regulatory pathways that cancers use to evade recognition by the immune system. Overactivation of these points in the tumor microenvironment (TME) promotes immune escape mechanisms. Consequently, checkpoint inhibitors, such as PD-1 receptor blockers and CTLA-4, have gained prominence as novel therapies that potentiate the cytotoxic function of T cells [12]. PD-1 blockade stimulates the antitumor response by increasing the activity of effector T and NK cells within the tumor and reducing the number and function of

tumor suppressor Treg cells, and abrogates the inhibition of kinases and recruitment of tyrosine phosphatases necessary for T cell activation [9,27].

Pembrolizumab is a humanized monoclonal antibody of the IgG4 class, which blocks the PD-1 receptor on T cells. Its action is to inhibit the interaction of PD-1 with PD-L1 and PD-L2 ligands, which enhances the immune response, especially in terms of anti-tumor activation [26,28,29]. PD-L1 expression is normally absent in cervical tissue, but is present in 95% of cases of cervical intraepithelial neoplasia (CIN 1-2) [20]. PD-L1 expression was observed in 34.4% of patients with cervical cancer, and varied by histologic type - 37.8% in squamous cell carcinoma, 28.6% in adenocarcinoma, and 16.7% in adenocarcinoma [29,30]. The first evidence of clinical activity of an immune checkpoint inhibitor in patients with advanced cervical cancer was obtained in the phase Ib KEYNOTE-028 trial. Twenty-four pretreated patients with PD-L1-positive advanced cervical cancer (96% squamous cell carcinoma) were enrolled in the trial and received pembrolizumab 10 mg/kg every 2 weeks for up to 2 years. The confirmed overall response rate was 17% (95% CI 5% to 37%), with a median duration of response of 5.4 months (95% CI 4.1 to 7.5) [13]. Compared to the placebo group, treatment with pembrolizumab resulted in an objective response rate of 68%[3]. The safety profile was favorable, with no grade 4-5 adverse events, and only two patients experienced grade 3 adverse events requiring discontinuation of therapy [13]. The most common serious adverse events included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infection (4.1%) [29]. In 2021, the FDA approved pembrolizumab as first-line therapy, used with chemotherapy, with or without bevacizumab, for patients with recurrent or metastatic PD-L1-expressing cervical cancer (CPS ≥1), and also as monotherapy in patients refractory to chemotherapy [3].

Nivolumab, like pembrolizumab, is a human monoclonal antibody of the IgG4 class that blocks PD-1, thereby increasing the immune response and enhancing anti-tumor T-cell activity [29]. A phase II study of NRG-GY002 evaluated its efficacy in patients with metastatic or recurrent cervical cancer with a dose of 3 mg/kg every two weeks. Median survival was 14.5 months, and survival rates at one and two years were 78% and 50%, respectively [22]. Nivolumab is now also approved for the treatment of other cancers, such as melanoma, squamous cell lung cancer, and clear cell renal cell carcinoma [29]. In conclusion, both pembrolizumab and nivolumab show promising anti-tumor activity with an acceptable safety profile in patients with recurrent or metastatic cervical cancer [29].

Cemiplimab is a humanized IgG4 monoclonal antibody that binds to PD-1, blocking its interaction with PD-L1 and PD-L2, which removes inhibition of the immune response and is associated with tumor reduction [11,29]. In the clinical trial, 304 patients were treated with cemiplimab every three weeks, and 304 received chemotherapy (including pemetrexed, vinorelbine, gemcitabine). Most patients had squamous cell carcinoma (77.8%). Median overall survival was 10.9 months in the cemiplimab group, compared to 8.8 months in those treated with chemotherapy (HR=0.69; p=0.0023). In the overall group, median survival was 11.7 months vs. 8.5 months (HR=0.65; p<0.001). Cemiplimab was also superior to chemotherapy in terms of progression-free survival and response rates [13,14]. Adverse events were fewer in patients treated with cemiplimab (56.7%) than with chemotherapy (81.4%), with no new toxicities [11]. On this basis, the FDA has given cemiplimab priority status for patients with recurrent or metastatic cervical cancer [3,13], and the EMA has approved it as monotherapy for patients after failed platinum-based chemotherapy [3].

Bevacizumab is a recombinant humanized IgG1-class monoclonal antibody directed against VEGF-A, which inhibits angiogenesis by blocking endothelial cell proliferation [13]. High levels of VEGF correlate with cervical cancer progression [31,32]. Bevacizumab has been used to treat advanced cervical cancer in combination with chemotherapy, which extended median survival from 12 to 17 months [12,13]. Studies have confirmed the superior efficacy and long-term tolerability of this therapy [12]. Despite its relatively good tolerability, some side effects have been reported, such as hypertension, gastrointestinal perforations, thrombosis, delayed wound healing, fistulas, and nephrotic syndrome [28].

Adoptive T-cell therapies represent an innovative immunotherapeutic approach for the treatment of HPV-associated cancers. They involve the isolation, expansion, and modification of a patient's T cells ex vivo, followed by their re-adoption, often after initial myeloablative treatment to facilitate cell engraftment [5,9]. The main strategies are tumor-infiltrating lymphocyte (TIL) therapy, genetically modified TCR receptor therapy, and chimeric antigen receptor T cells (CAR-T) [9]. Clinical studies have shown that TCR-T can

effectively recognize and destroy cervical cancer cells that express these antigens. In a clinical trial, TCR-T therapy showed the ability to induce an immune response and reduce tumor mass in some patients [22]. TIL therapy uses heterogeneous populations of lymphocytes isolated from the tumor, and preliminary studies indicate sustained responses in some patients [9]. TCR-T therapy relies on genetic modification of T lymphocytes to recognize specific HPV-related tumor antigens, such as E6 and E7 [7,33]. CAR-T therapy relies on the construction of synthetic receptors that enable T cells to directly recognize and destroy tumor cells [9]. Preliminary data indicate that CAR-T therapy can induce a potent cytotoxic response against tumor cells, although toxicity and the tumor's immunosuppressive microenvironment pose challenges [34]. In conclusion, immunotherapies, especially checkpoint inhibitors and CAR-T cell adoptive therapies, are promising treatment options for cervical cancer, offering hope for improved clinical outcomes in patients with advanced and refractory cancer.

Conclusions

Cervical cancer remains a major public health problem, despite significant advances in prevention, diagnosis, and treatment. The disease develops gradually, often over many years, providing an opportunity for effective prevention and early detection. A key role in the etiology of cervical cancer is played by chronic infection with human papillomavirus (HPV), especially oncogenic types 16 and 18. The introduction of HPV vaccination is considered one of the most important steps in primary prevention, which in the long term can almost eliminate this cancer. Unfortunately, the effectiveness of vaccination programs and cytological and molecular screening depends on the level of implementation, public awareness, and access to medical care. In terms of the treatment of advanced cervical cancer, chemoradiotherapy, combining radiotherapy with cisplatin, remains the standard. Patients with recurrent or metastatic disease receive systemic treatment - chemotherapy based on a combination of paclitaxel and cisplatin or carboplatin, often supplemented with bevacizumab, a monoclonal antibody that inhibits tumor angiogenesis. In recent years, there has been increasing hope for immunotherapy, especially using checkpoint inhibitors (e.g., pembrolizumab), which have shown efficacy in some patients with high PD-L1 expression. The future of cervical cancer therapy lies in the further development of targeted therapies and personalized strategies based on the molecular profile of the tumor. Clinical trials of new drugs and drug combinations are still ongoing, offering hope for further improvements in treatment outcomes. Nevertheless, to effectively reduce morbidity and mortality, systemic measures are needed - intensifying educational programs, increasing access to vaccination and screening, and closing the gap in access to modern therapies. A comprehensive and integrated approach, including prevention, diagnosis, and treatment, is the basis for an effective fight against cervical cancer on a population scale.

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