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IMMUNOTHERAPY IN THE TREATMENT OF CERVICAL CANCER

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Abstract: CC is one of the most prevalent types of cancer among women and represents a major challenge for public health worldwide. New therapeutic approaches, such as immunotherapy based on *checkpoint* inhibitors, have offered promising alternatives for the treatment of this cancer, especially in advanced cases or those that do not respond to conventional treatments. The aim is to discuss the importance of immunotherapy in the treatment of cervical cancer. The article consisted of a narrative literature review carried out through data collection in articles published in the SciELO, PubMed and VHL databases from 2019 to 2024 in Portuguese and English. Immunotherapy, including checkpoint inhibitors such as anti-PD-1 and anti-PD-L1, represents a significant advance in the treatment of CC, especially for advanced cases resistant to conventional treatment. In addition, emerging inhibitors, such as anti-CTLA-4, have shown potential in clinical trials. The development of new immunotherapies, such as combinations of *checkpoint* inhibitors and therapies that directly stimulate the immune system, as well as the exploration of emerging *checkpoints*, opens up new therapeutic possibilities. Personalizing treatment based on specific biomarkers, such as PD-L1 expression, tumour mutational load and the presence of specific genetic alterations, offers greater safety and efficacy, making it possible to identify patients who are more likely to respond to immunotherapy. The continuous development of immunotherapies, the identification of new checkpoints and the use of specific biomarkers strengthen the prospect of safer and more effective treatments, expanding therapeutic possibilities and improving patients' quality of life
Keywords: Cervical Cancer; HPV; Immune Checkpoint Inhibitors

INTRODUCTION

Cervical cancer (CC) is the second most common neoplasm among women, with a growth rate of approximately 28.6% of new cases in recent years, representing a serious public health problem worldwide[1]. In Brazil, CC is the third most common tumor in the female population, with approximately 626,000 new cases per year, second only to breast and colorectal cancer[2].

The disease is characterized by the disordered replication of the organ's lining epithelium, compromising the underlying tissue (stroma), as well as the ability to invade contiguous or distant structures and organs[3]. UCC develops slowly and has symptoms such as intermittent vaginal bleeding or bleeding after sexual intercourse, abnormal vaginal discharge and abdominal pain related to urinary or intestinal complaints in more advanced cases[4].

Among the associated factors that favor the occurrence of the disease are early onset of sexual activity, older age, multiple partners, smoking and, above all, infection with Human Papillomavirus (HPV), especially the carcinogenic serotypes 16 and 18, which are responsible for around 70% of cervical cancer cases, as well as serotypes 31, 33, 45, 52 and 58, which also have oncogenic potential[5-7]. Low socio-economic and educational levels have also been identified in studies as a determining factor in the incidence of the disease[1-3].

Current standard treatments for UCC include radiotherapy, chemotherapy and/or surgical resection[4,6]. Among the chemotherapy options, the best regimen for recurrent or metastatic UCC is the combination of cisplatin, paclitaxel and bevacizumab, with an overall response rate of 48% and a median survival of 17 months. However, these drugs have significant side effects and limited efficacy against advanced disease[8-9].

As UCC progresses, it can promote an immunosuppressive microenvironment and

neutralize the host's anticancer immunity. Thus, approaches to reverse suppressive immune environments and enhance effector T-cell function are likely to increase the success of immunotherapy against CC [10]. Immunotherapy represents a new method for treating cancers dependent on the immune system's natural ability to recognize and eliminate tumor cells directly. This therapeutic option offers an alternative for recurrent or metastatic cases, as demonstrated by the recent approval of the antibody blocking apoptosis or programmed cell death protein 1[11].

The therapeutic potential can be increased by combining it with antigen-specific immunotherapy approaches, such as vaccines or adoptive cell transfer, to boost the host's cellular immune response by targeting HPV--positive cancer cells[12]. With the recent introduction of immune *checkpoint* inhibitors that release the brakes on immunosuppression, the evidence for immunotherapy in the treatment of CC has finally been established[13]

Therefore, there is a need for research into this approach in gynecological cancers and the possibility that immunotherapy could become part of the therapeutic scenario for gynecological malignancies. The aim of this study was to discuss the importance of immunotherapy in the treatment of cervical cancer.

METHOD

This research consisted of a narrative literature review carried out by collecting data from articles published in the *Scientific Electronic Library Online* (SciELO), *Publisher Medline* (PubMed) and Virtual Health Library (VHL) databases between 2019 and 2024, in Portuguese, English and Spanish. To guide the choice of publications and selection of content, the following health science descriptors (DeCS) were used: cervical cancer, HPV and immune *checkpoint* inhibitors, combined using the Boolean operators *OR* and *AND*.

The inclusion criteria were indexed full--text articles that addressed the proposed theme and were available online. Book chapters, monographs, dissertations, theses, editorials, repeated and incomplete articles, abstracts and research that was not related to the aim of this study were excluded.

The data collected was analyzed using the thematic proposal and the criteria listed above, and based on these, the main articles were selected using the PRISMA methodology (Figure 1), which allowed for screening and eligibility of the chosen works. After selection, an interpretative reading of the publications was carried out to gather the relevant content to provide a theoretical basis for the study.

RESULTS AND DISCUSSION

TUMOR ANTIGENS AND THEIR RECOGNITION BY THE IMMUNE SYSTEM

Some tumors manage to develop in immunocompetent individuals, raising questions about the efficiency of anti-tumor immunity. This phenomenon suggests that cancer cells can escape immune surveillance, particularly T lymphocytes, which are essential in cellular immunity[14,15]. T lymphocytes mature in the thymus, where they differentiate into helper (CD4+) and cytotoxic (CD8+) T cells, which recognize specific antigens presented by the MHC molecules of antigen-presenting cells[16]

The activation of T cells is important in the defense against infections and tumors and involves several steps. First, contact is required between antigen-presenting cells (APCs) and T lymphocytes, where antigen receptors and co-stimulatory molecules interact. This initial interaction triggers the production of cytokines, such as interleukin-2 (IL-2), which promotes the multiplication of effector and memory T cells. IL-2 also activates regulatory T cells, which help to restore immune homeostasis, demonstrating the need for rigorous control of the immune response[16,17].

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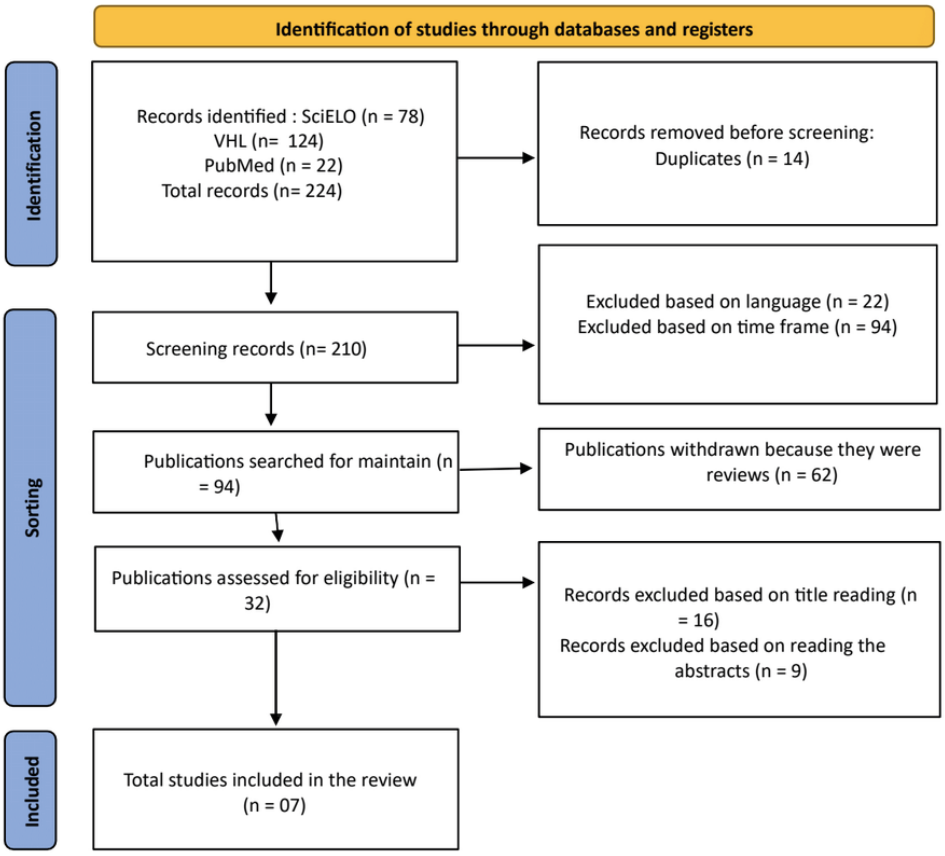

Figure 1 - Flowchart of the search for papers
Source: Author, 2024

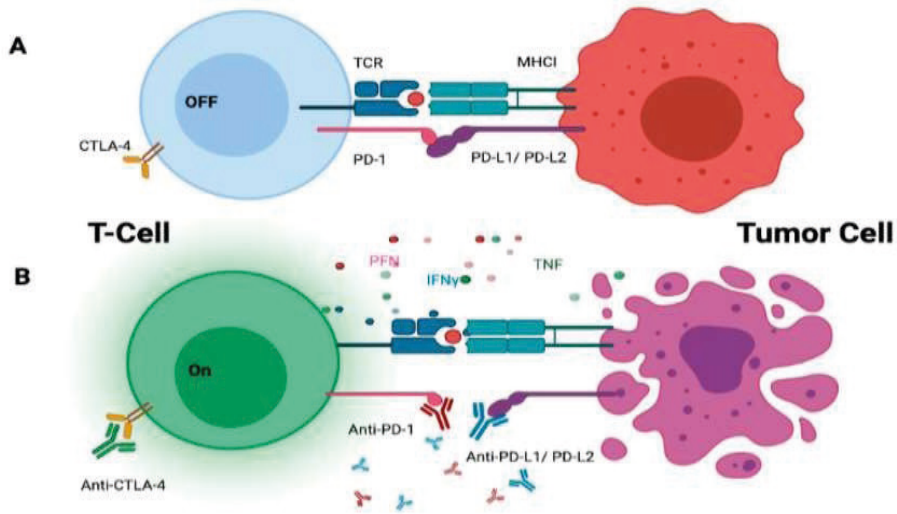

Figure 2 - Schematic illustration of the mechanism of action of PD-1, PD-L1 and CTLA4 checkpoint inhibitors (A) Programmed cell death receptor 1 (PD-1) is expressed on sensitized immune cells (T cells in representation). Binding of PD-1 to its B7 family of ligands, programmed death ligand 1 (PD-L1) or PD- L2 results in the suppression of antigen-specific T cell immune responses. Similarly, CTLA4 (cytotoxic T-lymphocyte-associated protein 4) is a protein receptor that functions as an immune checkpoint and negatively regulates immune responses. (B) Blocking antibodies to PD-1 or PD-L1 or CTLA4 reverses this process and increases anti-tumor immune activity. This ultimately leads to the release of cytolytic mediators such as perforin and granzyme, TNF and IFNα, causing further tumor destruction. TCR, T-cell receptor; MHC, major histocompatibility complex.
Source: Fatima et al. 2022[20].

This control occurs through proteins called "*checkpoints*", such as CTLA-4 and PD-1, which regulate the activation of T cells. Ligands for these proteins can be expressed in tumor cells, acting as an escape mechanism that reduces the anti-tumor immune response, favoring tumor progression. The expression of these molecules in tumor cells is therefore an important mechanism that prevents the destructive action of T cells against the tumor[17].

Studies with immunized animals have shown that it is possible to develop a specific response against tumors, confirmed by the identification of antigens such as MAGEA1[18]. In the early 2000s, the hypothesis emerged that the immune system not only protects against tumors, but also influences their immunogenicity, and can fight or promote cancer[14].

This process takes place in three phases: elimination, where the immune system eliminates tumor cells asymptomatically; equilibrium, where residual tumor cells are kept dormant; and escape, when tumor cells develop mechanisms to avoid the immune system, resulting in accelerated growth and symptoms[15].

Several mechanisms favor tumor escape, such as impaired antigen presentation, low MHC expression, modulation of apoptosis and production of immunosuppressive molecules (IL-10, TGF-β)[16]. The activation of regulatory T cells, myeloid suppressor cells and the expression of co-inhibitory proteins (CTLA-4, PD-1) also contribute to this process. This context has led to the development of anti-tumour therapies that block these mechanisms, promoting "immune normalization", restoring the immune response against tumours with greater efficacy and fewer adverse effects[17].

New immunotherapy strategies, such as the use of monoclonal antibodies and vaccines with tumor antigens, represent alternatives to traditional immunotherapies. As opposed to indiscriminate amplification of the immune response, these specific approaches seek to direct the immune system against the tumor, minimizing side effects. Examples include the use of monoclonal antibodies such as anti-CD20 and Her2/neu, as well as dendritic cell vaccines and adoptive cell therapy, which increases the activation and expansion of cancer-specific T cells[18].

MAIN IMMUNOTHERAPIES FOR THE DIAGNOSIS AND TREATMENT OF CERVICAL CANCER

Checkpoint-blocking immunotherapies, especially those that act on the PD-1/PD-L1 and CTLA-4 receptors, have become a promising approach in the treatment of advanced cervical cancer, especially for metastatic cases that are resistant to other therapies. These immunotherapies work by unblocking the body's innate immune response against the tumor by inhibiting proteins that suppress the activity of anti-tumor T cells[19]. In Figure 2, the CTLA-4 and PD-1/PD-L1 immune checkpoints are highlighted in the interactions between T cells, dendritic cells and tumor cells.

In cancers such as CC, which marked by immune escape mechanisms, the use of immunotherapies represents an important innovation. These drugs aim to restore the immune system's ability to identify and destroy tumor cells, favoring the fight against the tumor without the exclusive need for chemotherapy, with significant results in terms of overall survival (OS) and progression-free survival (PFS) in some patients[19,21].

Pembrolizumab, a PD-1 inhibitor, is one of the most studied immunotherapies in the treatment of CC. It has shown particular efficacy in prolonging the lives of patients with tumors that express high levels of PD-L1. Studies indicate that, in patients with high expression of this biomarker, pembrolizumab has the potential to significantly increase survival and reduce disease progression, when used alone or in combination with chemotherapy[18].

This response is observed mainly in patients who have a favorable immunological profile, with a higher expression of PD-L1, which facilitates the unblocking of the immune response and the action of T cells against the tumor. However, the efficacy of this immunotherapy in patients with low PD-L1 expression is still limited, indicating the need for therapeutic combinations or alternative approaches for these cases[21].

Another relevant agent is cemiplimab, which also acts to block PD-1. Studies have shown that cemiplimab has positive effects on overall survival in patients with UCC, especially in those with high PD-L1 expression. This immunotherapy has been shown to be effective in controlling resistant or recurrent UCC, offering a new alternative for patients with tumors refractory to conventional treatments[19].

Clinical data show that cemiplimab can be especially useful in patients with specific tumor characteristics, making it a valuable option when the response to standard treatment is insufficient. Nivolumab, another PD-1 inhibitor, is also being explored and has shown positive response rates in CC, further expanding the therapeutic possibilities for the disease[18,19].

In order to optimize treatment and expand the benefits of immunotherapy in UCC, new immunological targets, such as TIGIT, VISTA and LAG-3, are being investigated. These new immunological *checkpoints* play a crucial role in modulating the tumor microenvironment and inhibiting anti-tumor immune activity, reinforcing the mechanisms of escape from UCC[16].

Studies show that the elevated presence TIGIT and VISTA is associated a worse prognosis and shorter survival in patients with CC, indicating that these markers could be potential targets for future therapies. The inhibition of TIGIT and VISTA, in combination with traditional PD-1 and PD-L1 inhibitors, could amplify the immune response, offering new perspectives for personalized treatments[18].

These emerging *checkpoints* have the potential to complement PD-1 and PD-L1 inhibitors, increasing treatment efficacy and improving the immune system's ability to control tumor progression. The multiple *checkpoint* approach is a strategy that aims to attack the tumor through different escape routes, minimizing the possibility that the cancer will find ways to avoid the immune response[17]. In the case of HPV-positive tumors, the activation of additional *checkpoint* pathways, such as TIGIT and VISTA, further intensifies the immunosuppression of the tumor microenvironment, making it more difficult for the immune system to act against tumor cells[19].

In addition, the combination of immunotherapies with conventional treatments, such as chemotherapy, is being tested with promising results. The integration of immunotherapies with chemotherapeutic agents can increase the sensitization of the tumor to the immune response, providing better clinical results, especially in patients who do not respond well to immunotherapy alone[16]. Clinical trials with combinations of pembrolizumab and platinum-based chemotherapy have shown significant benefits in terms of tumor control, broadening treatment possibilities and providing a more comprehensive approach to UCC[17].

Selecting patients based on biomarkers, such as PD-L1 expression and other checkpoints, is essential for maximizing the effectiveness of immunotherapy treatments. These biomarkers help identify which patients are more likely to respond positively to treatment, allowing for a more personalized and effective approach[18]. Patients with high PD-L1 expression have benefited from immunotherapies such as pembrolizumab and cemiplimab, while for those with low expression, combination therapies with chemotherapeutic agents or other immunotherapies are being explored as alternatives[19].

FINAL CONSIDERATIONS

Immunotherapy with *checkpoint* inhibitors represents an important advance in the treatment of cervical cancer, particularly for patients in advanced stages or who do not respond to conventional treatments. By stimulating the immune response against tumor cells, these immunotherapies have proven effective in prolonging survival and controlling the progression of the disease. The introduction of new inhibitors and research into emerging checkpoints offer additional alternatives that broaden the therapeutic range, providing new options for patients who previously had few alternatives.

The personalization of treatment, based on specific biomarkers such as PD-L1, combined with the continuous development of immunotherapies, strengthens the prospect of more targeted and safer therapy. This advance not only expands therapeutic possibilities, but also contributes to improving patients' quality of life by offering treatments that meet the specific needs of each immunological profile. In this way, *checkpoint* immunotherapy is consolidating itself as a transformative approach in the fight cervical cancer, promoting a more robust immune response adapted to the characteristics of each case.

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