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Monoclonal Antibody Therapies for HPV-Associated Cervical Cancer: A Literature Review

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A B S T R A C T

Cervical cancer is a malignancy in gynecology attributable to human papillomavirus (HPV) infection with high prevalence and mortality caused by persistent infections of hr-HPV 16 and 18. HPV with various virulence factors can evade the immune system and integrate its genetic material into the host cell DNA. HPV replication only occurs in differentiated cells in the upper layer of the mucosal epithelium or skin developing into cancer. Globally, approximately 70% of patients diagnosed with cervical cancer present at an advanced or late stage causing therapy to be ineffective. The use of HPV-specific monoclonal antibodies for therapy with cervical cancer, as an alternative or complement will give new insight into managing the patients. The development of monoclonal antibodies having potential as an alternative therapy began to be used as a therapy in the advanced, recurrent, persistent or metastatic cervical cancer. This review specifically discusses monoclonal antibodies that have been approved by FDA for therapy against cervical cancer. In clinical trials, adding bevacizumab to combination chemotherapy extended median overall survival by 3.7 months in patients with recurrent, persistent, or metastatic cervical cancer. Pembrolizumab significantly prolonged progression-free and overall survival compared to placebo when combine to chemotherapy (with or without bevacizumab) in similar patient populations. Likewise, tisotumab-vedotin demonstrated greater over chemotherapy as second-line or third-line therapy for recurrent cervical cancer. Therefore, this article review aims to describe the types and roles of monoclonal antibodies that have potential to be used as a single or combination therapy especially chemotherapy for patients with cervical cancer.

1. Introduction

Cervical cancer is one of the most prevalent malignancies in gynecology. This cancer is caused by Human Papillomavirus (HPV) infection, which is transmitted through sexual contact with a high prevalence and mortality in worldwide. According to GLOBOCAN 2022, cervical cancer ranks 8th worldwide, with Asia experiencing the highest burden (1.795 deaths) and Indonesia facing the second-highest incidence and mortality rates among women's cancers.[1] Human Papillomavirus (HPV) infection is a major cause of cervical cancer and is responsible for approximately 5% of all cancer cases worldwide.[2] This is due to limited access to vaccination, screening, diagnosis, and treatment or therapy. Cervical cancer is a cancer caused by persistent infection with high-risk HPV.[3] Hr-HPV types 16 and 18 are the cause of 70% of cervical squamous cancer as the most frequently occurring type of cervical cancer.[4] DNA of HPV integration into the epithelial cell genome causing mutations into cancer.[5] Therefore, immunity against HPV depends on the production of antibodies through vaccines.[6] The HPV vaccine effectively prevents HPV infection with efficacy up to 99% when given before the first exposure to HPV.[7] However, the HPV vaccine cannot treat existing HPV infection. The development of monoclonal antibodies has great potential as an alternative therapy.[8]

Monoclonal antibodies have a broad application in development of immunotherapies for various diseases, including viral infections and cancer.[9] They function by binding to tumor and cancer antigens, thereby stimulating an immune responses. The first monoclonal antibody approved by the US FDA for cancer therapy was Rituximab in 1997 for non-Hodgkin lymphoma, followes by Trastuzumab for HER2-positive breast cancer.[10] In cervical cancer, monoclonal antibodies serve as an alternative to standard chemotherapy or chemoradiotherapy, particularly for patients with advanced, recurrent, or metastatic disease, based on evidence from randomized clinical trials and regulatory approvals.[3–5] For example, pembrolizumab has

demonstrated improved progression-free survival in PD-L1-positive cervical cancer patients.[3] The mechanisms of monoclonal antibodies in cervical cancer include inhibiting angiogenesis (anti-VEGF, e.g., bevacizumab), enhancing immune checkpoint blockade (anti-PD-1/PD-L1), and targeted drug delivery via antibody-drug conjugates (ADCs).[11–13]

Bevacizumab, in combination with chemotherapy, has gained approval for advanced cervical cancer, showing efficacy in halting early progression and reducing treatment-related side effects compared to chemotherapy alone.[6] Clinical trials have consistently shown that combining monoclonal antibodies with chemotherapy enhances efficacy, reduces toxicity, and improves survival rates in these patient populations.[8] Monoclonal antibodies like bevacizumab, pembrolizumab, and tisotumab vedotin represent critical advancements in cervical cancer therapy, particularly for recurrent, persistent, or metastatic disease where traditional chemotherapy offers limited survival.[11-13] Therefore, this paper explores the types and roles of monoclonal antibodies that have the potential to be used as a standalone or combination therapy for cervical cancer caused by HPV infection.

2. Methods

This literature review was conducted using a methodology that included selecting data sources or databases and applying criteria for choosing literature. The primarily used major biomedical and scientific databases, four databases were used in total like PubMed, ScienceDirect, ResearchGate, and Google Scholar to ensure we had a wide range of relevant information These various databases provide broad access to relevant literature on the oncogenesis of cervical cancer and potential monoclonal antibodies as alternative therapy treatments from preclinical until clinical trial phase 3. This review is based on accredited scientific articles published in the last 10 years. This strict criterion ensures our analysis of monoclonal antibodies as a cervical cancer therapy is both in-depth and current.

3. Classification and Characteristics of HPV

Human Papillomavirus (HPV) is a group of small dsDNA virusese, with genomes ranging from 7100bp to 8104bp, non-enveloped and possessing rotational symmetry.[14,15] HPV belongs to the family Papillomaviridae, classificafied under Kingdom Shotokuvirae, Phylum Cossavirieota, Class Papovaviricetes, and Order Zurhausenvirale.[2] Currently, over 400 HPV types have been identified based on DNA sequences comparison of L1, L2, E1, and E2 genes. *Papillomaviridae* is divided into five genera: *Betapapillomavirus, Mupapillomavirus Alphapapillomavirus, Gammapapillomavirus* and *Nupapillomavirus.*[14] High-risk HPV (hr-HPV), mainly from the *Alphapapillomavirus* genus, infect mucosal ephitelia nad include types such as HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82.[14] The HPV genome consist of three regions containing LCR (long control region), early (E), late (L).[16] The E region encodes the initial proteins for replication (E1, E2), transcription (E2), viral release (E4), and support of viral replication including the avoidance of the human immune system (E5) and sustained of epithelial cell growth and proliferation (E6, E7).[16]

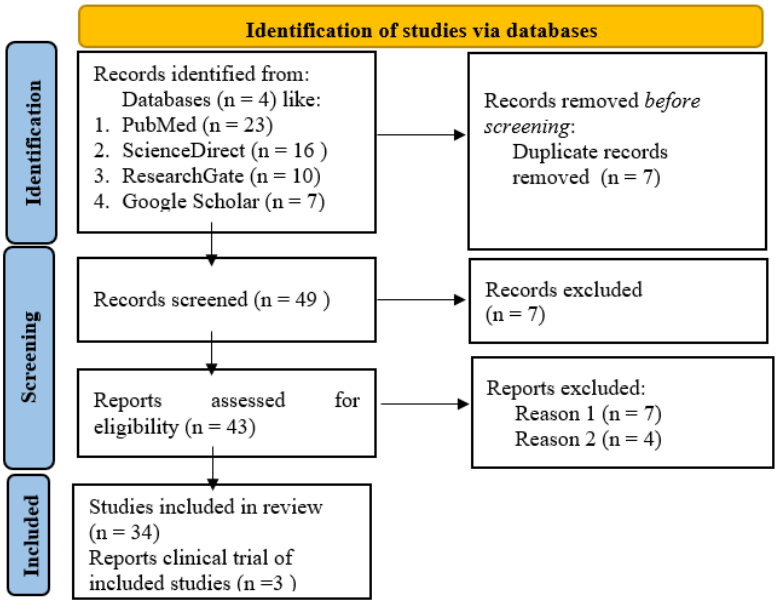

Figure 1. **PRISMA flow diagram ilustrating the study selection process for the literature review**

HPV genome typically contain 5-11 open reading frames (ORFs), with the L1 capsid protein as the main virulence factor.[14] Oncoproteins E5, E6 and E7 are crucial for cell transformation, with E6 and E7 being ideal targets for immunotherapy because they are consistently expressed in nearly all cervical cancer cells. The variability of E5–E7 indicate the oncogenic potential of the virus, while E4 determines the affinity for the route of transmission.[14]

The structure and expression patterns of HPV are highly relevant to antibody therapy. While E6 and E7 are ideal immunotherapy targets due to their constitutive expression in cancer cells, most monoclonal antibodies currently in clinical use such as bevacizumab, pembrolizumab, and tisotumab-vedotin target host factors or viral entry pathways rather than E6/E7 themselves. This is because direct targeting of E6/E7 with antibodies is technically challenging due to their intracellular localization and lack of surface exposure.[6] Instead, therapies often focus on host immune checkpoints (e.g., PD-1/PD-L1 targeted by pembrolizumab), angiogenesis (VEGF targeted by bevacizumab), or surface-exposed viral or tumor antigens (as in tisotumab-vedotin).[11-13]

4. Replication of HPV and Oncogenesis of Cervical Cancer

Tropism of HPV infection cells in keratinocytes from the layered epidermis of the human body.[14] Genome replication and assembly of HPV virions can only occur in cells that differentiate in the upper layer. The virus infects the basal layer of the epithelium that is the site of cell proliferation. Differentiation of HPV-infected cells induces HPV replication to progeny in the upper layer of the epithelium[14]. In the early phase, the HPV virion attaches to the cell via heparan sulfate proteoglycans (HSPG) on the basal membrane. So that HPV can enter the cell through endocytosis.[14] HPV genome replication is divided into 3 phases: establishment, maintenance and amplification. The viral genome replicates synchronously with cellular DNA during the maintenance phase in undifferentiated cells. Differentiation of HPV-infected cells allows replication of the virus in the amplification phase.[14]

Oncogenesis of cervical cancer begins when HPV integrates into the human genome. The continuous expression of oncogenic proteins E6 and E7 disrupts the p53 and pRb pathways, which then leads to the development of cervical cancer.[6] E6 and E7 are overproduced and crucial in altering the cellular function of epithelial cells. This leads to a precursor lesion, a cervical intraepithelial neoplasia, which develops over time into an invasive cancer.[12] HPV can induce hyperplasia, papillomatous and squamous wart cell lesions on the skin and various mucosal locations that are widespread in humans.[2] Cervical cancer can be classified into squamous cell carcinoma and adenocarcinoma.[17]

5. Immune Response to HPV Infection

Innate and adaptive immunity play an important role, especially cellular adaptive immunity in fighting HPV infection.[18,19] HPV genetic material will be recognized by PRRs such as TLRs 2, 7 and 9 result in increased IFN-α, IFN-β and ILN-1α. HPV16 can induce IFN-γ.[18] The initial response also involves NK cells and T cells. The development of precancerous lesions is controlled by cellular adaptive immunity. CD8+ and CD4+ specific T cell infiltrates are found in healed HPV lesions. The oncoproteins E6 and E7 of HPV16 and 18 have peptides at their epitopes stimulating CTL response.[14] About 90% of all HPV infections can be inhibited by the immune system. An adequate immune response is affected by the presence of different protein variants in each type of HPV due to both genetic subtypes and differences in transcription and translational rates.[14] Treg lymphocytes play an important role in suppressing the immune response to HPV. Persistent HPV16 infection caused CC and genital warts that enlarge and recurrent after treatment showing an increase in the number of Treg lymphocytes.[18] HPV is also capable of affecting the immune system by altering the expression of certain host genes. HPV16 can deregulate immunity by suppressing the function of TLR9, an innate sensor for dsDNA.[20] E6 and E7 inhibit the acetylation of K310 from p65 so that signal transduction by NF-κB is inhibited as well as decreased production of pro-inflammatory cytokines specifically TNF-α, IL-1, IL-12, IL-6, IL-2, IL-8.[19]

6. Standard Therapy of Cervical Cancer

The type of cervical cancer therapy depends on the stage of cancer development, the patient's health condition, the presence of side effects, and the purpose of therapy.[21] Surgery is a common therapy in treating various early-stage cancers. Radical hysterectomy performed laparoscopically shows an elevated frequency of recurrence, infertility and urinary bladder dysfunction in the long term.[21] Chemotherapy in cervical cancer is usually given as adjuvant therapy after surgery when a poor prognostic tumor increases the risk of disease recurrence. Cisplatin chemotherapy in patients in the early stages shows increased resistance, thus reducing the effectiveness of chemotherapy.[23] Currently, monoclonal antibody therapy has begun to be used in advanced cervical cancer combined with chemotherapy.[22] The development of new and better therapies because multidrug resistance affects the success of chemotherapy with conjugate antibodies.[23]

External Beam Radiation Therapy (EBRT) is the most frequently used radiotherapy for cervical cancer. Although there are many side effects of radiotherapy such as toxicity, abdominal cramps diarrhea, pelvic pain, skin, lymphedema and sexual dysfunction.[21] In addition, among patients with stage IIA-IIIB cervical cancer, radiotherapy resulted in a

response rate where 20–50% of women experienced failure to inhibit progression of locally advanced disease.[22] Combination therapy with monoclonal antibodies can increase the effectiveness radiotherapy in inhibiting cervical cancer progression.[22]

7. Monoclonal Antibodies and Their Mechanisms as Cervical Cancer Therapy

Monoclonal antibodies (mAbs) are derived from single-cell clones that have cleaved to produce antibodies *in vitro* and *in vivo* against specific tumor antigens.[24] Monoclonal antibodies aim to replace antibodies present in the body and imitate the immune response against pathogens and cancer cells. There are different types of mAb such as murine, chimeric, humanized, human, mAbs, as well as antibody-drug conjugates (ADCs) and bispesific mAbs.[10,24] Technique mAbs production through hybridoma by Georges K¨ohler and C´esar Milstein in the year 1975.[24] Hybridization between antibody-producing B cells and myeloma cells that are immortal. The most common isotype used in cancer therapy is IgG.[10] Monoclonal antibodies have great potential to play a role as a targeted on-therapy as well as immunotherapy against hr-HPV infection in cervical cancer. Currently, there is still a lot of development preclinical and clinical testing of various monoclonal antibodies that have the potential to be therapeutic agents in cervical cancer.[22]

Cervical cancer therapy methods depend on the stage and size of the tumor including radical hysterectomy, radiotherapy or chemotherapy. However, the life expectancy of people with cervical cancer is still low due to chemotherapy resistance and recurrence. Chemotherapy can cause disruption of the cellular level and balance of the immune system. Therefore, a new strategy is needed to increase the life expectancy while reducing the toxicity of chemotherapy, which is a combination of therapy and monoclonal antibodies with various inhibition mechanisms.[10,11] Therapy on-target inhibits angiogenesis and proliferation of cancer cells through mitosis. In addition, increased cellular factor expression (VEGF) is associated with the rate of angiogenesis and malignant development. Anti-VEGF factors inhibit the binding of VEGF to its receptors thereby preventing increased angiogenesis of cancer cells. A variety of monoclonal antibodies that have been approved in the experimental to treat cervical cancer, prevent its development in the early stages and reduce the side effects of other therapies.[10] In addition, in 20% of cases metastatic epithelial malignancy after the use of these mAbs for 1 to 2 years results as part of an immune response.[25]

7.1 Bevacizumab as Anti-VEGF

Bevacizumab (Avastin) is a humanized monoclonal antibody, with approximately 93% human and 7% mouse protein in its sequence. This chimeric structure is important because it reduces immunogenicity compared to fully murine antibodies, lowering the risk of immune reactions and allowing for repeated dosing in patients.[26,27] The administration of bevacizumab inhibits VEGF-A which inhibits angiogenesis and proliferation of cervical cancer cells and was approved by the FDA in 2014.[11] Recurrent or metastatic cervical cancer will become so severe and increasingly difficult to cure.[11] VEGF promotes angiogenesis, playing a role as a promoter of cervical cancer progression. Bevacizumab is a humanized anti-VEGF monotherapy antibody having efficacy as a single drug for recurrent disease in previously treated patients.[11] Most patients who develop recurrent have previously received cisplatin with radiotherapy, which reduces the effectiveness of cisplatin at the time of recurrence.[11] Oncogenesis involves the oncoprotein hr-HPV16 E5 regulating the overexpression of VEGF through the EGFR-MEK1/2 and PI3K-AKT pathways playing a role in tumor development. Epidermal gene growth factor receptor (EGFR) is highly expressed in 80% of cervical cancer tumors, so being a target for anti-viral oncoprotein E6/E7/E5 can prevent cancer progression.[28]

Bevacizumab is usually given in combination with other chemotherapy that can improve survival rate in patients with advanced cervical cancer so that the therapeutic effect is stronger than single chemotherapy.[26] Bevacizumab recognizes and neutralizes the main isoform of VEGF and block VEGFR from binding to it and inhibits the formation of new blood vessels. The progressive growth of the tumor depends on angiogenesis regulated by VEGF. The VEGF pathway facilitates tumor growth by increasing proliferation, migration, invasion, and vascular permeability. Development of lesions CIN being cervical cancer is highly relies on angiogenesis and high levels of VEGF expression is associated with a worse outcome for the patient. VEGF is an attractive therapeutic target of anti-angiogenesis, Bevacizumab has been tested in cervical cancer.[24] Bevacizumab increased grade 3+ hypertension, thromboembolism, and gastrointestinal fistulas, especially in irradiated patients, no chemotherapy backbone superiority, and limited subgroup benefits (poor prognosis per Moore criteria).[11]

The mechanism of inhibition of growth and development by Bevacizumab against cervical cancer is consists of two main types: anti-vascular and anti-angiogenesis. Anti-vascular as the initial effect of inhibition of Bevacizumab against VEGF causes tumor blood vessel regression resulting in a reduction in the size of cervical cancer tumors. Anti-angiogenesis in the form of inhibition of the growth of new and recurrent tumor vessels. In cervical cancer, Bevacizumab has been approved to treat recurrent,

persistent, or metastatic cervical cancer in combination with the chemotherapy drugs paclitaxel and cisplatin or topotecan given intravenously, increasing life expectancy by an average of 3.7 months.[30] The efficacy of Bevacizumab is determined by Progression-Free Survival (PFS) with histopathological confirmation and Overall Survival (OS). The higher the PFS indicating the better the efficacy of monoclonal antibody therapy.[11] Adverse effect of Bevacizumab are associated with embolic and gastrointestinal fistulas. The addition of Bevacizumab to combination chemotherapy in patient with persistent, recurrent, or metastatic cervical cancer (MCC) was correlated with an enhancement of 3.7 months in median OS.[11]

7.2 Pembrolizumab as Anti-PD-1/PD-L1

Pembrolizumab is an effective treatment for metastatic or unresectable cervical cancer that has progressed during chemotherapy, specifically in patients with tumors programmed death 1 (PD-L1) positive.[12] The anti-PD-1 specific monoclonal antibodies like Pembrolizumab are humanized monoclonal antibodies that are effective in inhibiting the development of all types of cervical cancer. In 2018, the FDA approved pembrolizumab as a second-line therapy for advanced cervical cancer patients that has been resistant to chemotherapy. In 2021, it approved as a first-line therapy for cervical cancer. Overexpression of PD-1 on the surface of activated T lymphocytes spesifically Treg, alters immune homeostasis.[31] Pembrolizumab works by programming the death of cervical cancer cells via PD-1. Pembrolizumab has two stable variables, PD-1 binding variables with great affinity and specificity, preventing PD-1 interactions. In patients with advanced cervical cancer, a 33% recovery rate was shown for 10.3 months after therapy along with vaccines and Pembrolizumab.[12] The conjunction of pembrolizumab with the GX-188E DNA vaccine showed significant improvement compared to monotherapy.[32]

The effectiveness of Pembrolizumab in inducing the recovery of tumor-specific CTL in the tumor microenvironment. Reactivating the anti-tumor immune system has been shown to have anticancer effects on recurrent and metastatic cervical squamous carcinoma. The efficacy of pembrolizumab as a therapy for stage III-IVA cervical cancer was higher when compared to the placebo group. Clinical trials phase 3 show improvement in PFS that is statistically significant in the entire population of patients with stage III-IVA cervical cancer and the Pembrolizumab group showed significantly greater efficacy, with a longer duration of effect. The most common adverse reactions that appear include higher anemia and neutropenia. The anti-PD1 pembrolizumab has demonstrated efficacy and primarily agent adverse effects of low severity when used as single therapeutic in patients with cervical cancer. The most common adverse events were anemia and neutropenia.[12]

7.3 Tisotumab-Vedotin (TFTV) as anti-Tissue Factor

The limited treatment for recurrent cervical cancer especially after first-line therapy fails present a significant challenge and a serious threat to a patient's survival. So that patients with recurrent, second or third-line therapy with Tisotumab-vedotin resulted in more effective than chemotherapy in phase 3 clinical trial. Tisotumab-vedotin is a humanized IgG1 monoclonal antibody approved by the FDA in 2021 as an Antibody-Drug Conjugates (ADCs) in cervical cancer with its high specificity and affinity after phase 2 clinical trial.[39,8] The use of ADCs arises from the need to enhance the antitumor effects of conventional treatment, leveraging its specificity to target antigens to enhance antitumor activity. Tisotumab-vedotin was able to reduce the therapy led to a 30% lower risk of death for patients with recurrent or metastatic cervical cancer. Results of phase 3 clinical trials in 502 adult women showed significantly longer overall survival (OS) and represented a 30% lower risk of death in patients with metastatic or recurrent cervical cancer compared to chemotherapy. TFTV as a therapeutic option has been shown to extend life expectancy who have progressed after initial treatment. Progression-free survival and objective response also favored TFTV.[13]

Tisotumab vedotin is an antibody drug conjugate targeting Tissue Factor (TF) using covalent binding proteases and the Microtubule-Disrupting Agent Monomethyl Auristatin E (MMAE) on monoclonal antibodies.[13] Tissue factor is elevated in several solid tumors, including recurrent cervical cancer. The mechanism of tisotumab vedotin as an anticancer is caused by the binding of ADCs to cancer cells expressing TF followed by the internalization of the ADC-TF complex and the release of MMAE. MMAE will interfere with cancer cell microtubules and DNA disruption that actively divide causing cell cycle termination and cell death in the form of apoptosis. Testing *in vitro* shows Tisotumab-Vedotin also mediates phagocytosis and antibody-dependent cellular cytotoxicity. Among patients with recurrent or metastatic cervical cancer after previous systemic therapy, treatment with tisotumab vedotin resulted in significantly greater efficacy than chemotherapy. The most common adverse reactions (≥25%) to therapy was decreased hemoglobin, discontinuation due to toxicity, peripheral neuropathy, conjunctivitis, increased aspartate and alanine aminotransferase, nausea, fatigue, decreased sodium, epistaxis and constipation.[33]

8. Potential and Challenges of Monoclonal

Antibodies in Cervical Cancer

The potential and challenges of monoclonal antibodies in cervical cancer have been shaped by advances in cancer genomics, immunology, and molecular biology.[8] Monoclonal antibodies can accelerate tumor cell death by recognizing tumor-associated antigens and stimulating antitumor immune responses, with benefits such as modulation of macrophage polarization, enhanced anti-cancer immunity, and reduced tumor proliferation. However, immunotherapy is also associated with adverse effects, including skin disorders such as mucositis and pruritus, anemia, and neutropenia.[8] Anemia and neutropenia as the most common adverse observed in clinical trials of pembrolizumab and tisotumab-vedotin. [12,13]

Antibodies are molecules that can identify tumor cells as a result of their specific recognition of tumor antigens. They are useful for delivering drugs that activate the immune system and for detecting tumors in their early stages.[34] In a natural infection in immunocompetent individuals, antibodies can neutralize the HPV virus when reinfection occurs. However, a person who is immunocompromised is unable to fight an HPV infection.[24]

A monoclonal antibody for cervical cancer therapy that has been used is the result of the development of the same type of antibody but with different disease therapy targets such as Bevacizumab (Avastin).[10] Some of the functional limitations of monoclonal antibodies as cancer therapy are their ability to penetrate solid tumors (pre-cancerous) and low interactions with the immune system. The primary challenge with therapeutic mAbs is drug resistance. To overcome this, we need a better understanding of their mechanism of action and to explore modifications such as conjugating them with other compounds, alterations in the Fc region of antibodies can increase the activation of NK cells and macrophages in combination with conventional therapies.[10]

E6/E7 oncoproteins from HPV, ideally immunogenic due to constant cervical cancer expression, evade direct monoclonal antibody targeting because of their intracellular (nuclear or cytoplasmic), inaccessible to surface-binding antibodies like bevacizumab (anti-VEGF), pembrolizumab (anti-PD-1), and tisotumab vedotin (anti-tissue factor ADC).[11-13] Therefore, future antibody development may aim to directly target E6/E7 or their downstream pathways to enhance therapeutic efficacy.[22]

9. Limitations

This review exclusively addresses three FDA-approved monoclonal antibodies bevacizumab, pembrolizumab, and tisotumab vedotin that have undergone clinical trials in metastatic, recurrent cervical cancer patients. Those agent require combination with other therapies like chemotherapy for demonstrated efficacy and lacking evidence in early-stage, non-recurrent disease and necessitating combinations with chemotherapy. Monotherapy applications of these agents demand additional investigation beyond current combination trial evidence. Numerous other monoclonal antibodies remain under development for cervical cancer.

10. Conclusion

Monoclonal antibodies work to recognize specific receptors on cancer cells. Humanized monoclonal antibodies approved by the FDA show the ability to inhibit the development of cervical cancer in patients in phase 3 clinical trials including Bevacizumab, Pembrolizumab and Tisotumab-vedotin. Bevacizumab as an anti-VEGF generally combined with chemotherapy can increase therapeutic effect and efficacy. Pembrolizumab works by programming cancer cell death via PD-1 in persistent, recurrent or metastatic cervical cancer. Monotherapy in cervical cancer using Pembrolizumab has good efficacy with a low level of toxicity. The latest monoclonal antibody as a immunotherapy for metastatic or recurrent cervical cancer is Tisotumab-vedotin. It is effective in increasing life expectancy and more effective by triggering cancer cell apoptosis in metastatic or recurrent cervical cancer.

These agents deliver precise mechanisms anti-VEGF inhibition of angiogenesis (Bevacizumab), PD-1 checkpoint inhibitions (Pembrolizumab), and antibody-drug conjugate delivery (Tisotumab vedotin) lower risk of progression or death risk, superior response rates of chemotherapy, and integration into standard care for advanced disease. Despite manageable toxicities like hypertension or anemia. By prioritizing hard clinical endpoints over vague "potential," this analysis equips clinicians with evidence to optimize survival in HPV-driven gynecologic malignancies. Bevacizumab excels in first-line therapy for recurrent, persistent, or metastatic cervical cancer when combined with chemotherapy, extending median overall survival by 3.7 months. Pembrolizumab suits PD-L1-positive patients in first-line settings alongside chemotherapy (with or without bevacizumab), prolonging PFS and 24-month OS. Tisotumab vedotin outperforms chemotherapy in second- or third-line recurrent disease post-platinum failure.

11. Author Contribution

D.J. conceptualized the idea and concept. conceptualized the research idea, developed the concept and outline, collect data and analysis, drafted, revised the manuscript and final approval. A.Y. provided supervision (supporting), guidance on idea development, conceptualization, and manuscript writing.

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