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Cervical cancer: Treatment & Therapies

VITTHAL S. KALYANKAR , RAHUL MOHAN, RAJENDRA KAWDE,

First author, Co-author, Co-author ,

Nandkumar Shinde College Of Pharmacy, Vaijapur

Tah: Vaijapur , Dist: Chhatrapati Sambhajinagar ,

Pincode:423701, State: Maharashtra, Country: India,

ABSTRACT

Cervical cancer is the fourth most common cancer in women worldwide and causes more than 300,000 deaths worldwide. The causative agent of cervical cancer is a persistent infection with high-risk subtypes of the human papillomavirus. And viral oncoproteins E5, E6, and E7 cooperate with host factors to induce and maintain the malignant phenotype. Cervical cancer is a largely preventable disease and early detection is associated with lower survival rates. Significantly improved. Indeed, in high-income countries with established vaccination and screening programs, it is a rare disease. However, the disease is deadly for women in low- and middle-income countries Who, due to limited resources, often present with advanced and incurable diseases.

Treatment options include surgical procedures, chemotherapy and/or radiation therapy, alone or in combination. This review describes the initiation and progression of cervical cancer and takes an in-depth look at the benefits and challenges facing current therapies for cervical cancer, followed by a discussion of promising and effective new therapies for the treatment of the cervical cancer, including targeted immunotherapies. Therapies. , combination therapies and gene treatment approaches.

Keywords : cervical cancer, targeted therapy, combination therapy,crisper-cas9

INTRODUCTION

In 2020, about 10 million deaths related to cancer were reported, making it one of the leading causes of death in the world. Even if this number is is projected to increase worldwide, this increase is expected to occur mainly in low and middle income countries (LMIC), as they currently face the greatest challenges in the fight against cancer [1, 2].

Worldwide, cervical cancer is the fourth most common cancer in women after breast cancer, colorectal cancer and lung cancer and accounts for 600,000 new cases. Cases and 340,000 deaths per year [1,3,4]. It is important to note that approx 83% of all new cervical cancer cases and 88% of all deaths occur in LMICs [3,4]. Indeed, cervical cancer is the leading cause of cancer death in 36 countries, including regions such as sub-Saharan Africa, Latin America and India [1,4]. This burden must be

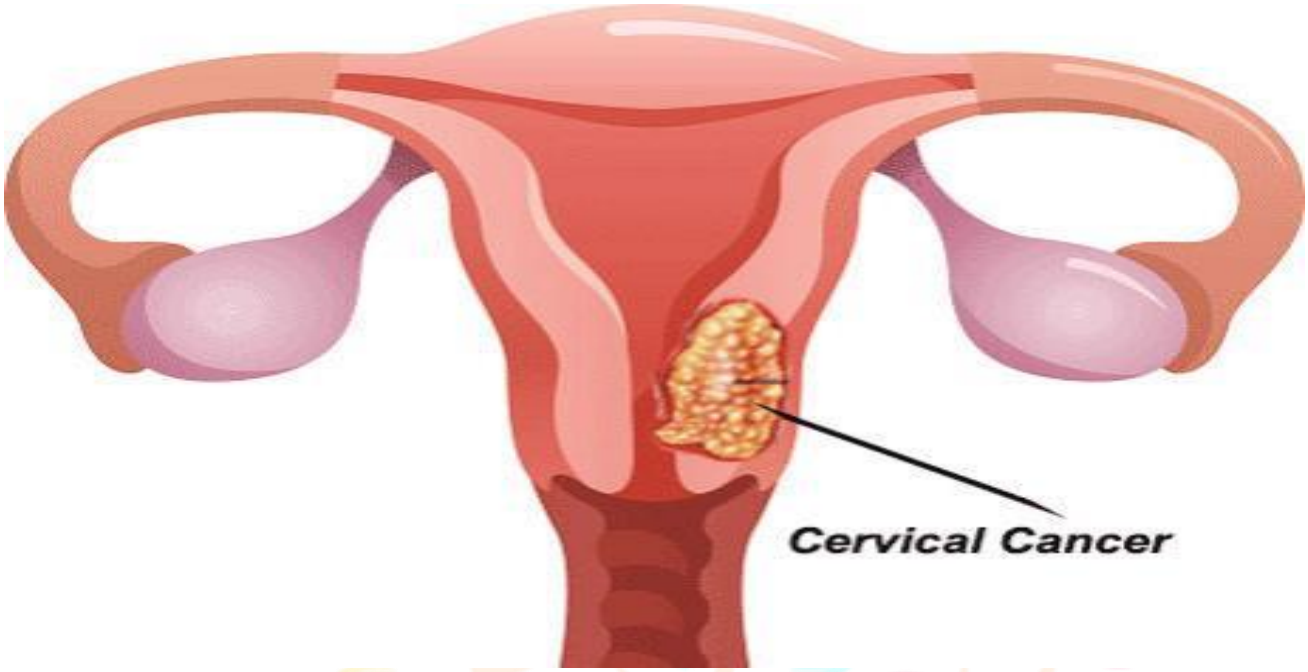
contextualized in terms of socio-economic conditions, health care infrastructure and competing health needs, which are not only risk factors for this disease, but also have a significant impact on its prevention and management. It is worrying that, despite significant advances in our understanding of cervical cancer as a potentially preventable disease, there have been no major improvements in patient survival and that, consequently, the burden of disease remains high [3] .The most important etiologic agent of cervical cancer is high-risk human papillomavirus (HPV) infection [5]. Indeed, persistent infection with high-risk HPV types is responsible for 99.7% of cervical cancer cases [6,7]. The link between HPV and cervical cancer has been established over the past 30 years based on the discovery of HPV type 16 in cervical cancer tissue by Harald zur Hausen [8,9]. It is estimated that HPV infects approximately 291 million women worldwide, with a particularly high prevalence in women under 25 [10]. The estimated global prevalence of HPV in women with normal cytology is 11.7%, but there is considerable geographic variation, with sub-Saharan Africa having the highest HPV prevalence (24.0%) [11]. Sub-Saharan Africa is also highly affected by HIV, with more than 70% of all HIV-positive people in the world residing in Sub-Saharan Africa [12].

There is convincing evidence that women are infected with HIV They have an increased risk of persistent infection with several types of HPV in one Early age (13-18 years) [13-15]. These factors lead to an increased risk of developing cervical cancer at an early age [16,17]. Indeed, people infected with HIV are at risk Six times more likely to develop cervical cancer compared to the general population [18]. Also, in one The study conducted in South Africa between 2001 and 2009, the increase in the incidence of cervical cancer can be explained by the increase in the number of HIV infections observed during this period [16]. In addition, the increase in the number of HIV-positive women who receive antiretroviral therapy leads to an improvement in life expectancy and therefore these women must be properly screened, since they are at greater risk of developing cancer cervical [19].

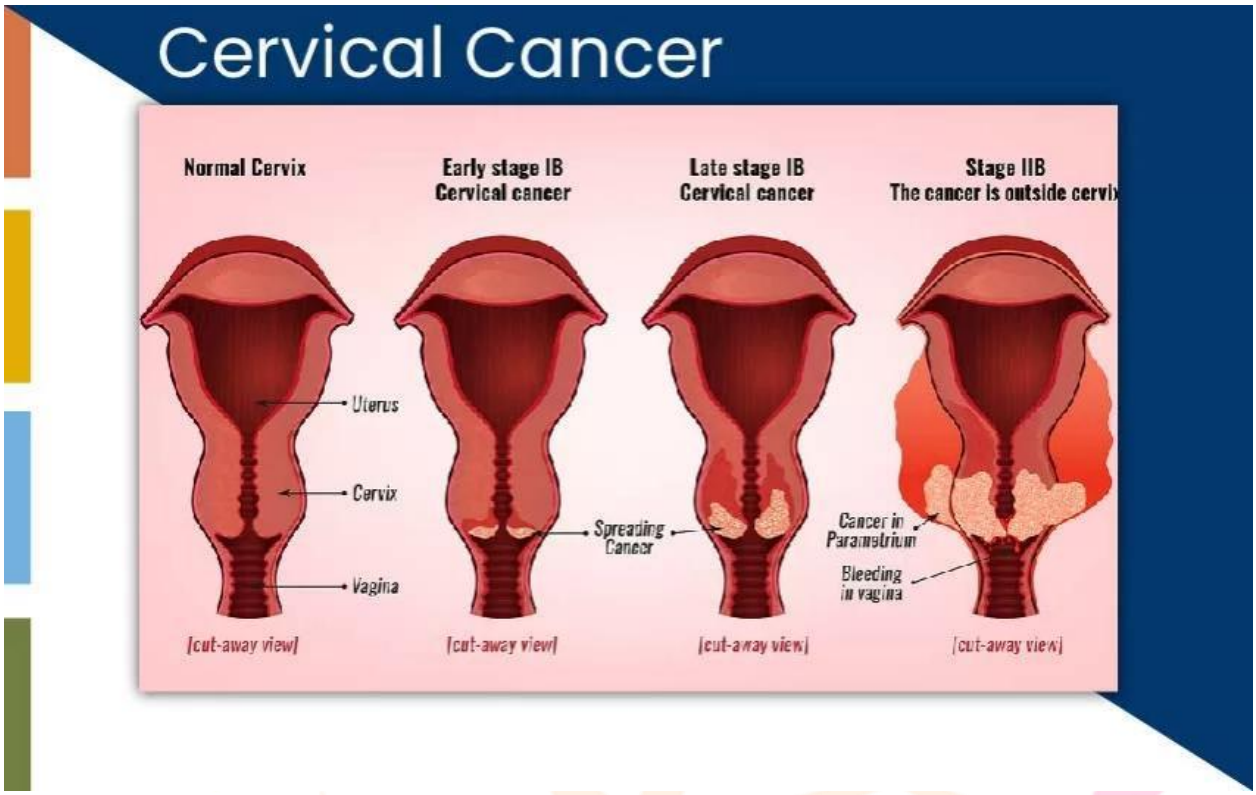
Initiation and progression of cervical cancer

Cervical cancer begins in the cervix, which is the narrow opening of the uterus and connects to the vagina through the endocervical canal [20]. The cervix is divided into ectocervix and endocervix. While the ectocervix is covered with epithelial cells Stratified squamous, the endocervix consists of simple columnar epithelial cells. Stratified, columnar squamous epithelium forms the junction Squamo-cylindrical in the endocervical canal. The area where these regions meet is called the “transformation zone,” which consists of the metaplastic epithelium that replaces the columnar epithelium of the. endocervix. This area is the most likely place for the development of cervical cancer, because it is a major site of premalignant transformation.

From persistent HPV infection [20]. There are two main histological subtypes of cervical cancer, squamous cell carcinoma (SCC). And adenocarcinoma. While SCC develops from cells Squamous cells of the ectocervix and account for approximately 75% of cervical carcinoma cases , adenocarcinoma arises from mucus-producing gland cells in the endocervix [21]. Since SCC is the major subtype, this review Will focus on the description of its progression.During the progression of CTS, the squamous cells of the cervical epithelium undergo dysplastic changes after HPV infection, and these precursor lesions infections can lead to the development of cervical cancer [23]. Indeed, in South Africa, a number of cross-sectional analyzes have found that between Between 60 and 80% of women are positive for HPV infection, while an age-standardized rate of 30.2 cases per 100,000 women are diagnosed with cervical cancer [24].



During the establishment of a persistent infection, HPV can be integrated into The host genome, with 80% of HPV 16 and 100% of HPV 18 positive cervical carcinomas showing viral integration [25,26]. It should be noted that a small percentage of HPV positive women develop cervical cancer in the absence of viral DNA integration and in these cases HPV DNA remains in its episomal form [27]. Viral proteins E5, E6 and E7 contribute to the induction and maintenance of the cervical cancer phenotype by exploiting the host cell machinery [28]. Indeed, E5 does this by regulating and interacting with other host growth factor receptors, epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor β, and receptor β of platelet-derived growth factor 1 [29]. E5 has also been shown to prevent apoptosis after DNA damage by disrupting the host FAS receptor and degrading the pro-apoptotic factor BAX [30,31]. In addition, E5 contributes to the immune evasion of infected host cells by reducing the surface expression of major histocompatibility complex (MHC) class I and II, as well as the surface receptor CD1d [32-35] . E6 and E7 promote cervical cancer by disrupting cellular checkpoints and cooperating with host factors, including tumor suppressors and promoters (36,37). For example, E6 and E7 mediate malignant transformation through degradation of p53 and inactivation of the retinoblastoma tumor suppressor protein (pRb), respectively (38,39). When HPV DNA integrates into host cells, significant loss of the HPV genome, including the E5 coding sequence, occurs [40]. Integration of viral DNA, however, results in constitutive expression of E6 and E7 because the E2 repressor protein cannot bind to viral regulatory regions (URRs) due to methylation, or its open reading frame. (ORF) is disrupted [41,42]. In cervical cancer resulting from HPV integration into host cells, E5 is not an essential player and E6 and E7 are responsible for driving and maintaining the malignant phenotype [38, 41].



Cervical cancer disease management

Primary and secondary prevention strategies for cervical cancer remain essential to reduce the burden of the disease and much has been written on this topic [44]. Therefore, the purpose of this review is to focus on treatment options for cervical cancer. Early-stage cervical cancer is often asymptomatic and can be diagnosed during a routine screening or pelvic exam. The most common symptoms include heavy or abnormal vaginal bleeding, especially after intercourse [45,46]. Some women may experience vaginal discharge that may be thin, mucoid or purulent and smelly, but it is rarely seen in isolation from other symptoms [47]. In advanced disease, patients may experience lower extremity edema, arm pain, and even pelvic or back pain [48]. In addition, bowel and/or complaints related to the bladder, such as changes in pressure or the passage of urine and/or feces through the vagina, indicate the involvement of the bladder and the rectum, respectively [48]. A pelvic examination is administered to patients with symptoms of cervical cancer and includes visualization of the cervix and vaginal mucosa and a biopsy if an abnormality is noted [49]. The cervix can be normal when the disease is microinvasive or in the endocervical canal. In contrast, large tumors can appear to completely replace the cervix, and metastatic lesions can be identified by palpable and enlarged lymph nodes [3]. If a patient presents with a Pap test result that suggests a high-grade precancerous lesion (HSIL) or a recurrent low-grade cytology (LSIL), then a colposcopy is performed for a definitive diagnosis, and all suspicious lesions are biopsied for analysis. If a precancerous lesion is confirmed by colposcopy and/or biopsy results, a therapeutic process called large loop transformation zone excision (LLETZ) can be performed to remove precancerous cells and prevent cancer. The stage of cervical cancer is an important prognostic marker and is determined clinically, based on the size of the tumor and the extent of the pelvic extension and imaging[43]. It is important to note that the stage of the disease is determined at the time of diagnosis, and accurate staging is essential in planning treatment, advising patients on prognosis, and evaluating eligibility for research studies [3, 6].

4. Treatment of cervical cancer

As mentioned above, the stage and extent of progression of the cervical cancer determines the necessary treatment strategy and may include one or more surgical interventions, radiotherapy and chemotherapy .

4.1. Surgery

Surgery is a commonly used and effective technique to fight various cancers in the early stages because it involves the physical removal of cancerous tissue. However, it can also be used to remove metastatic tissue [50]. Currently, the types of operations performed to treat cervical cancer include total hysterectomy, radical hysterectomy, electrosurgical excision procedure (LEEP), conization, trachelectomy, and cryosurgery [39]. The choice of surgical intervention depends greatly on the stage of the disease and its extent [52]. Total hysterectomy with or without salpingo-oophorectomy (removal of one or both ovaries) remains the treatment of choice for infertile women. Radical hysterectomy is most often used for larger cervical cancer lesions (up to 4 cm in size) and involves complete resection of the uterus, cervix, parametrium and superior vaginal cuff [51]. Results of the Laparoscopic Approach to Cervical Cancer (LACC) trial found that radical hysterectomy performed laparoscopically was associated with an increased rate of recurrence, loss of fertility and potential long-term urinary dysfunction [53]. Therefore, radical hysterectomy with the open technique is the preferred method, especially for tumors larger than 2 cm. For women of reproductive age with early-stage disease, a more conservative treatment approach is needed, and fertility-sparing surgeries include LEEP, conization, and trachelectomy [51]. LEEP uses a thin thread to remove abnormal tissue from the cervix and can be performed under local anesthesia in low-cost clinical settings, such as in low- and middle-income countries.

4.2. Radiotherapy

Radiotherapy uses high-energy X-rays and is a mainstay of treatment in the management of cervical cancer [3,6]. The three types of radiation therapy currently used totreat cervical cancer are external beam radiation therapy (EBRT), intensity modulated radiation therapy (IMRT), and brachytherapy (internal RT). Advanced diagnostic tools such as computed tomography (CT) and magnetic resonance imaging (MRI) have also improved the assessment of the primary tumor, the extent of tumor invasion and metastasis, which has also improve radiotherapy planning [3,6]. In short, EBRT directs beams of high-energy radiation from outside the body to the tumor and is the most common form of radiation therapy used to treat cancer. IMRT, a more advanced form of Radiotherapy, involves the manipulation of radiation beams of photons and protons To match the shape of the tumor and is used for cancerous and non-cancerous tumors. Like IMRT, brachytherapy It spares nearby tissues by delivering a single high dose of radiation Tumor or by inserting a radioactive implant into the tumor site [6, 54].

Despite the significant progress in radiotherapy, many adverse effects are associated with this form of treatment, including diarrhea, abdominal cramps and pelvic pain, skin toxicity, lymphedema, and sexual dysfunction (55). Although there is a complete answer in 68.3% of patients with cervical cancer in stage IIA-IIIB, inter In 20 to 50% of women, radiotherapy alone fails to locally control disease progression [56,57]. To improve the effectiveness of radiotherapy,it is often used in combination with chemotherapy, especially for larger cervical cancer lesions (more than 4 cm in width) [58].

4.3. Chemotherapy

Chemotherapy is an integral part of the standard treatment regimen for cervical cancer and is usually administered as adjuvant therapy after surgery when the poor prognostic characteristics of the tumor increase the risk of disease recurrence, in conjunction with radiotherapy as previously mentioned and as an independent treatment. For cervical cancer. Locally advanced disease . The single most effective agent used since the last three decades to treat cervical cancer is cisplatin, an agent Platinum-

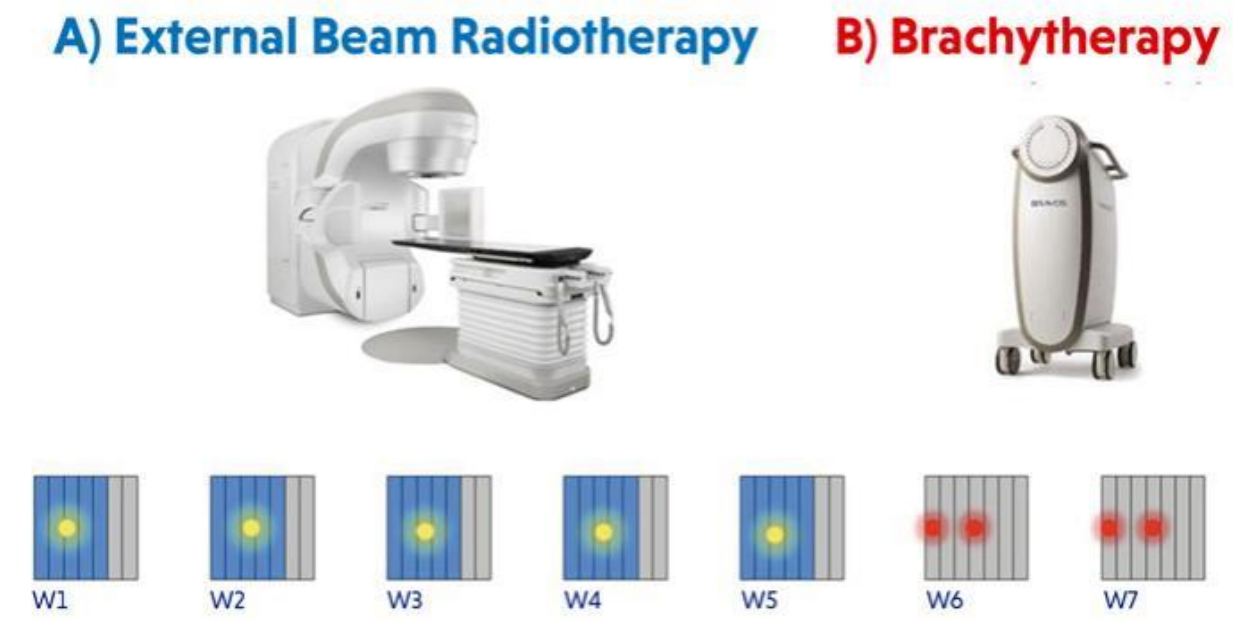
based chemotherapies [59]. However, despite the initial response of patients to cisplatin, an increase in resistance during treatment is often reported, reducing the effectiveness of chemotherapy. Of the second platinum line [60]. Later, studies showed that the combination of cisplatin with other agents is potentially more effective than single drug treatment [59,61]. Indeed, a study by Long et al. (2005) Showed that the response rate of cisplatin alone was 20%, combined with topotecan, but that increased to 39% [62]. Another one Study gave similar results when cisplatin is combined with paclitaxel [63]. Currently, topotecan, paclitaxel and others Chemotherapy without platinum, such as 5-fluorouracil and Bleomycin, so they are usually used in combination with cisplatin To treat cervical cancer. This results in a significant and clinically significant improvement in median survival time [59]. Chemotherapy is also often combined with radiation therapy (chemotherapy).

Radiotherapy) and is mainly used for locally advanced cervical cancer. This treatment regimen aims to reduce disease recurrence, but may result in adverse events and chronic morbidity. A systematic review and meta-analysis found that chemoradiotherapy improves overall and progression-free survival and reduces the risks of local and distant recurrence of cervical cancer [64]. Finally, palliative chemotherapy is used to improve the quality of life and alleviate the symptoms of the disease, even if it does not effectively reduce the size of the tumor [65,66]. The discovery and development of new and improved therapies is also important in relation to the multidrug resistance of cancer cells, which affects the success of chemotherapy (67).

5. Future outlook on cervical cancer therapies

Figure 1

Common schedule of chemoradiation for cervical cancer. Treatment starts with 5 weeks of external beam radiotherapy (A, blue bars) with concomitant weekly chemotherapy (yellow circles). In weeks 6 and 7, brachytherapy is applied (B, red circles).

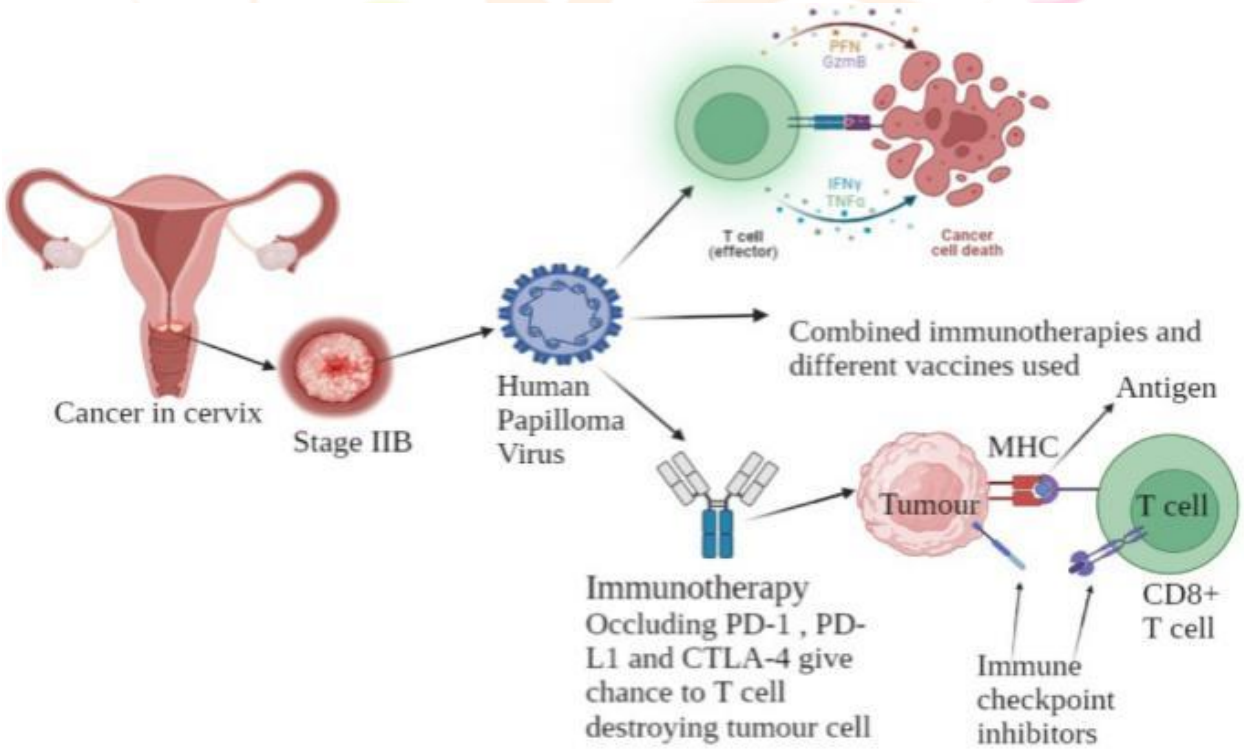


5.1. Immunotherapy for cervical cancer

Immunotherapy targeting HPV oncoproteins has been investigated as a new treatment for cervical cancer and has shown great promise. An advantage of this treatment is that it specifically targets precancerous and malignant dysplastic cervical epithelial cells that express HPV oncoproteins [68,69]. This approach has gained traction and led to many laboratory and clinical advances, including the development of vaccines, checkpoint blockade/inhibitors, and adoptive T-cell therapies for cervical cancer. These immunotherapies have varying degrees of success and many are currently in clinical trials [68,70].

An example of an HPV-16-specific therapeutic vaccine in a clinical trial found that it was able to target preinvasive dysplastic lesions and resulted in a 79% response rate in HPV-positive grade 3 vulvar intraepithelial neoplasia [71] . Other vaccines that specifically target the E6 and E7 oncoproteins of HPV-16 and -18 can be based on live vectors, which include viral and bacterial vectors, or based on peptides and proteins, [72]. To date, several phased clinical trials have been conducted for immune checkpoint inhibitors (ICIs) and tumor infiltrating lymphocytes (TILs) in cervical cancer with improved clinical efficacy [68.73]. ICI works by releasing the immunosuppressive brakes, Specifically programmed cell death 1 (PD-1), its ligands programmed cell death ligand1 (PD-L1) and programmed cell death ligand 2 (PD-L2), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [68,74]. PD-L1 is expressed On the surface of antigen-presenting cells and TILs, and it is suggested that Plays a role in the initiation and continuation of HPV infection in Decreased T-cell activity is rarely observed in normal cervical tissue, Even when adjacent to CIN or cancer cells. Due to the strong association between HPV infection and cervical cancer, PD 1 or its ligands are good targets for blockade, since they can interfere with the PD-1/PD-L1 inhibitory interaction and restore the T cell-mediated killing [75-77].] .

FDA-approved ICIs that target PD-1/PD-L1 include pembrolizumab, which is effective in PD-L1-positive solid cervical cancer tumors, and nivolumab, which is used to treat metastatic and recurrent cervical cancer [78-80]. . The checkpoint protein receptor CTLA-4 regulates the immune system by negatively regulating and inhibiting T cell activation, allowing T cells to respond to tumor cells and exhibit antitumor immunity [81,82] . Not surprisingly, blocking CTLA-4 has been shown to allow the body to overcome immune suppression associated with HPV-induced cancers. Indeed, ipilimumab, a



humanized monoclonal antibody targeting CTLA-4, induced significant immune activation in peripheral blood, although it did not induce a significant tumor response in breast cancer patients [83]. However, treatment with ipilimumab Only after chemoradiotherapy increased the antitumor response of cervical cancer, suggesting that this potential combination can provide A desirable immunological boost for patients at high risk of disease recurrence [84]. Combination of PD-1 and CTLA-4 receptor inhibitors, such as Nivolumab and ipilimumab respectively showed a Sustained clinical activity in recurrent or metastatic cervical cancer, regardless of status PD-L1. The adverse reactions reported for this combination were Manageable and consistent with previous reports of nivolumab and Ipilimumab [85].

Finally, the promising results of adoptive T-cell therapy (ACT) studied in B-cell malignancies and metastatic melanoma have led to the design of new studies in various malignancies, including cervical cancer [73]. This approach involves harvesting TILs from patient tumor tissues or peripheral blood, ex vivo expansion, and reinjecting them into the patient to effectively target cancer cells [70, 72]. LN-145 TIL, an ACT in an ongoing phase II trial, has shown a disease control rate of 89% and an objective response rate of 44%, although the trial is not yet complete and more is needed tests [70]. Based on the preliminary results of this trial, a phase I study is underway Which evaluates the potential of using LN-145 TIL followed by interleukin-2 (IL-2) for the treatment of patients with recurrent metastatic carcinoma of the cervix who have undergone non-myeloablative lymphodepletion [73]. Lymphopleting is a method to suppress the activity of lymphocytes and T cells before immunotherapy, since immunosuppressive T cells can prevent the complete eradication of established tumors [86].

The benefits of lymphopplementation include increased exposure to cytokine activation, improved recognition of low-affinity antigens, and reduced susceptibility to suppression by regulatory elements. [87]. Since ACT is a highly personalized approach, it can circumvent the use and thus limitations of chemotherapy in cervical cancer, but additional studies are needed [88]. In general, there is a shift towards the application of a combined approach to immunotherapies, either with other immunotherapies or with current existing therapies to achieve higher response rates [89].

5.2. Targeted therapy in cervical cancer

Chemotherapy agents kill cancer cells and rapidly dividing normal cells, leading to debilitating side effects such as anemia and alopecia [90]. Targeted therapies are specifically designed to inhibit Molecules, most commonly proteins, which are specifically expressed by Cancer cells and are responsible for controlling growth, Spread and spread of cancer [91]. Therefore, targeted therapies are expected to have increased efficacy and reduced adverse effects compared to current chemotherapies because they are more specific to cancer cells than to normal cells. A better understanding of the molecular mechanisms underlying cervical cancer has allowed researchers to identify factors involved in oncogenic pathways that constitute potential therapeutic targets. This has been particularly important for patients with metastatic or recurrent cervical cancer, as their prognosis is particularly poor (91). Targeted therapy also aims to target tumor drug resistance mechanisms, as this is a major challenge in the current therapeutic paradigm [67,90]. The following sections discuss the main oncogenic procedures most commonly used in the treatment of cervical cancer.

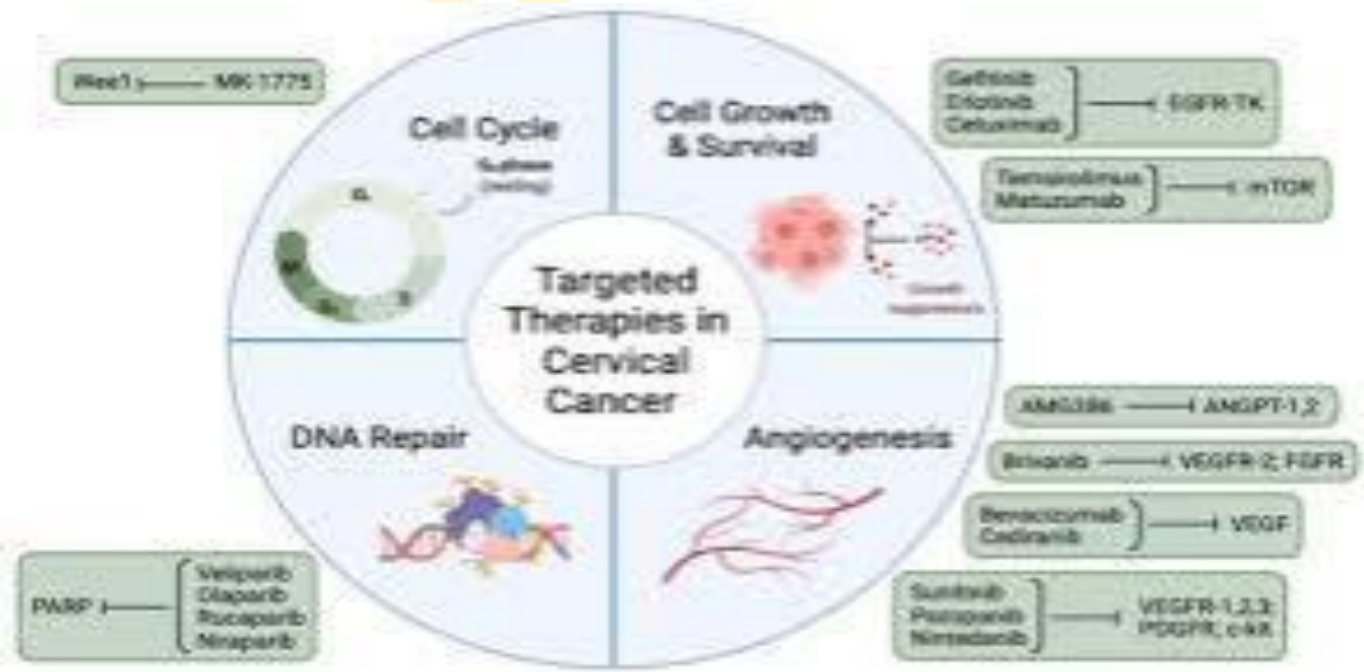
5.2.1. The cell cycle

The cell cycle is divided into four distinct phases that include checkpoints that ensure that the genetic integrity of cells is maintained during cell division. The four phases are: (1) G1 is a checkpoint where cells decide if the conditions are favorable for their DNA replication and if not, they enter quiescence/senescence (G0); (2) S is the point where DNA replication (synthesis) occurs; (3) G2 is a control point where cells verify that DNA replication is carried out with high fidelity; and (4) M (mitosis) is the point at which cells divide into two identical daughter cells. The transition between the four phases of the cell cycle is tightly regulated by cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors, and other kinases and phosphatases. Under favorable conditions, cyclin-CDK complexes are activated and phosphorylate substrates that allow cells to progress through the cell cycle. When conditions are not favorable, progression through the cell cycle is inhibited by CDKIs that inhibit proto-oncogenes and activate tumor suppressors to activate cell cycle checkpoints [92].

Mutations leading to inhibition And/or activation of these tumor suppressors or proto-oncogenes Therefore, they result in persistent proliferative signaling and the evasion of growth suppressors, which are key signs of cancer [93]. It is not surprising, the motors of the cell cycle are constitutively activated In

cancer cells have been identified as therapeutic targets. An example of such a target in cervical cancer is the tyrosine kinase Wee1 which in non-malignant cells acts as a tumor suppressor, but in cancer cells functions as an oncogene [94]. In response to DNA damage in nonmalignant cells, Wee1 prevents entry into mitosis by catalyzing a Inhibitory tyrosine phosphorylation of CDK1/cyclin B . which It allows DNA repair to maintain genomic integrity [95]. In cervical cancer, as in other types of cancer, the tumor suppressor p53 is lost or inactivated, leading to the disruption of the G1/S checkpoint and cells exploiting Wee1 activation of the checkpoint. G2/M control to repair any DNA damage, e.g. those caused by radiotherapy, to survive [96,97]. Indeed, Wee1 is upregulated in cervical cancer cells with p53 gene mutation, and its inhibition by the potent Wee1 inhibitor MK-1775 is an effective treatment strategy since it is able to selectively target cancer cells dependent on the G2 checkpoint. This causes cell death by mitotic catastrophe, as well as increased sensitivity of cervical cancer cells to chemotherapy and radiotherapy, which was explored in combination with MK-1775 .[96,98-100].

5.2.2. Cell growth and survival



Cervical cancer, like most other cancers, is associated with constitutive activation of growth factors and pro-survival signaling pathways.An example is the epidermal growth factor receptor (EGFR), which is a transmembrane tyrosine kinase receptor to which members of the epidermal growth factor family of extracellular protein ligands bind [101]. Ligand binding induces a conformational change in which EGFR forms a dimer and increases the catalytic activity of its internal tyrosine kinase. This results in autophosphorylation that activates a number of intracellular pathways that control cell division and survival, such as the Ras/Raf/mitogen-activated protein/extracellular signal-regulated kinase pathway and the phosphatidylinositol 3-kinase/ AKT. EGFR protein is overexpressed in many cancers where it affects signaling pathways to promote cancer cell proliferation, block apoptosis, activate invasion and metastasis, and stimulate tumor-induced angiogenesis [102]. For example, EGFR is overexpressed in approximately 70% of cervical squamous carcinomas, where it regulates growth, survival, proliferation and differentiation. Furthermore, the results of a systematic meta-analysis concluded that EGFR expression could be a predictive biomarker for reduced survival in cervical cancer patients . Therefore, anti-EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have been studied as single agents in cervical cancer patients. In a clinical trial, however, gefitinib and erlotinib both showed minimal activity as monotherapy, but were well tolerated.Furthermore, treatment with gefitinib resulted in stable

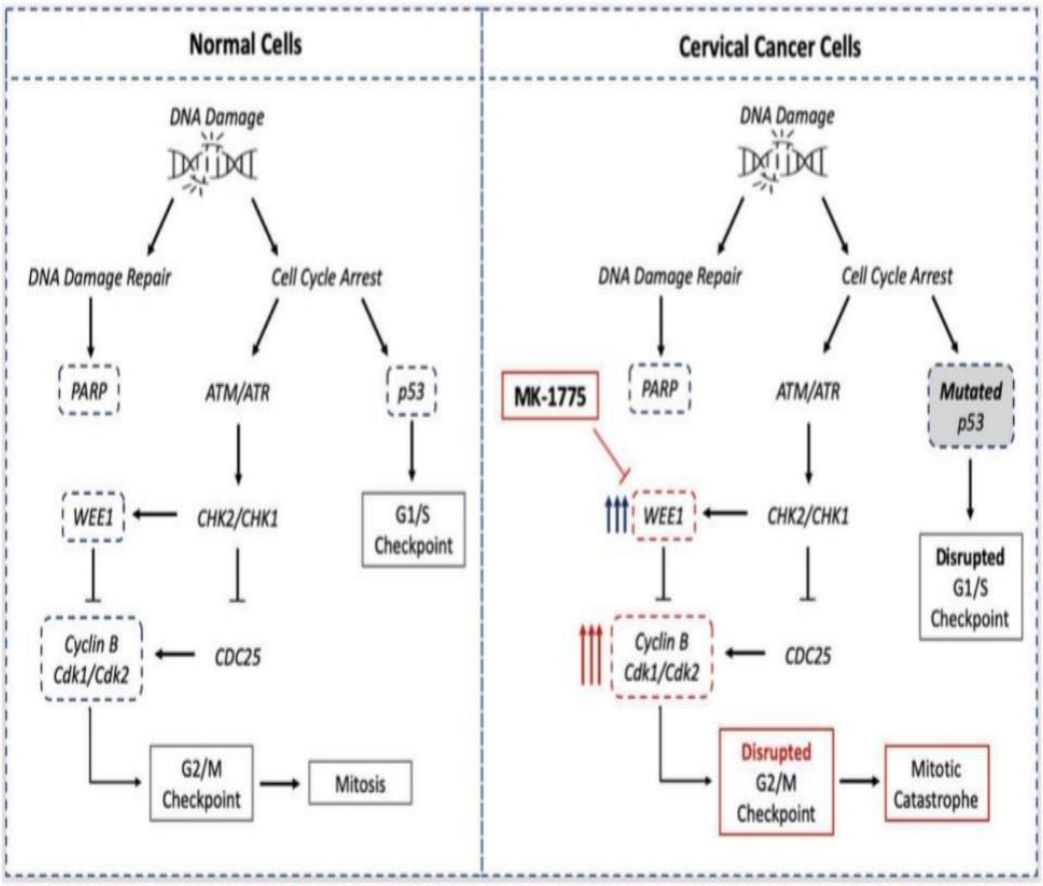
disease in 20% of patients and, when evaluated as maintenance therapy after chemoradiation, 67% of patients remained disease-free for 27 months after treatment . Furthermore, other experimental EGFR-specific monoclonal antibodies have shown a significant reduction of xenograft tumors in mice in combination with cisplatin, compared to single therapy .

In the end Combination with other therapies for the treatment of cervical cancer [91,]. This is consistent with the use of temsirolimus in other cancers to reduce the dose of radiotherapy or chemotherapy after conventional surgical procedures Due to the structural similarity between PI3K and mTOR, other rapamycin analogs are expected to be able to target PI3K/Akt and are currently being investigated .

5.2.3. Angiogenesis

When tumors are larger than 1-2 mm3, they are not able to remove nutrients by capillary diffusion in the tumor microenvironment. Its further growth depends on angiogenesis Which is the formation of new blood vessels to sprout and remodeling of pre-existing vascular networks into a more complex vasculature. . The main orchestrators of this process are members of the vascular endothelial growth factor (VEGF) family that exert their biological effects by binding to cell surface receptors (VEGFR). The VEGF pathway plays an important role in angiogenesis during embryonic development and wound healing, as well as in cancer where it facilitates tumor growth by increasing endothelial cell proliferation, invasion, migration and permeability vascular The progression of CIN lesions in cervical cancer is also highly dependent on angiogenesis, and VEGF overexpression is associated with a poor prognosis [91]. Therefore, VEGF is an attractive therapeutic target and to date, a number of anti-angiogenesis drugs, including bevacizumab and pazopanib, have been developed and tested in cervical cancer Bevacizumab is an antibody that recognizes and neutralizes the major isoforms of VEGF, preventing VEGFR from binding to them and therefore inhibiting the formation of new blood vessels .Pazopanib is a small molecule TKI that inhibits angiogenesis and cervical cancer growth by targeting multiple tyrosine kinases, including VEGFR . Angiopoietin, ANGPT1 and ANGPT2 are integral in the formation, remodeling, maturation and maintenance of blood vessels and are highly expressed and Secreted by cervical cancer cells .Therefore, they are also promising therapeutic targets for the inhibition of angiogenesis and AMG386, a ANGPT inhibitor is currently being explored as a targeted therapy for cervical cancer. Although preliminary data on anti-angiogenic agents in cervical cancer are promising, phase III trials are needed to improve our understanding of the value of agents that target angiogenesis in patients with cervical cancer..

5.2.4. DNA repair



As mentioned before, radiation therapy is a major form of treatment for neck cancer. The reason is that radiation therapy causes high levels of DNA damage and the DNA damage response (DDR) is compromised in cervical cancer cells and therefore have a reduced ability to repair this damage of DNA and, consequently, undergo cell death by apoptosis.Indeed, the common HPV integration site is found in RAD51B, a well-characterized DDR gene, and E6 and E7 oncoproteins inactivate p53 and pRb which are key mediators of DDR. Other mechanisms to inhibit cervical cancer have also involved targeting other cell cycle checkpoint regulators and DDR factors such as poly ADP-ribose polymerases (PARPs) [96]. PARP-1 and PARP-2 are involved in the repair of DNA double-strand breaks Has been shown to improve homologous recombination and inhibit it Cytotoxicity of DNA-damaging agents . High levels of PARP activity were observed in HPV-positive cells and in cisplatin-resistant HeLa cells, and PARP inhibitors increased the cytotoxic capacity of cisplatin in these cells synergistically .Together, these results suggest that targeting PARP activity may be beneficial for the treatment of cervical cancer. Indeed, PARP inhibitors have been reported to induce synthetic lethality in DDR-impaired cancers and have been investigated for the treatment of cervical cancer. Clinical trials have investigated PARP-specific targeted therapies, veliparib and olaparib, in combination with chemotherapeutic agents in patients with advanced, persistent or recurrent cervical cancer .

5.3. The role of combination therapy in cervical cancer

Cervical cancer is a complex and resistant disease and current therapies have limited efficacy, in part due to tumor resistance to current monotherapies [91]. A combination of Therapies may have advantages over monotherapies because they are More likely to inhibit multiple and/or redundant signaling pathways Essential for the survival of cervical cancer cells [64]. In addition, the combination of Therapeutic strategies reduce intensity, cost, number of cycles and Side effects associated with high

doses of monotherapy [64,91]. Combination with other therapies for the treatment of cervical cancer [91]. This is consistent with the use of temsirolimus in other cancers to reduce the dose of radiotherapy or chemotherapy after conventional surgical procedures .Due to the structural similarity between PI3K and mTOR, other rapamycin analogs are expected to be able to target PI3K/Akt and are currently being investigated [91].

Furthermore, while a complete response was achieved in 28 of 220 patients who received this combination, a complete response was achieved in only 14 of 219 patients who received only chemotherapy .Despite some promising results of combining chemotherapy with targeted drugs, the results of a number of trials that have studied this combination for the treatment of cervical cancer are inconclusive and therefore more research is needed. Positive clinical evidence from combined therapeutic approaches used in other cancers can help this research.

5.4. Genetic approaches to the treatment of cervical cancer

Emerging evidence has revealed that new genome editing systems and genetic approaches capable of deleting HPV E6 and E7 genes are promising strategies for the treatment of cervical cancer [39]. Some examples include the CRISPR/Cas9 system (short palindromic protein associated with regularly clustered interspersed repeat) and RNA interference (RNAi) .

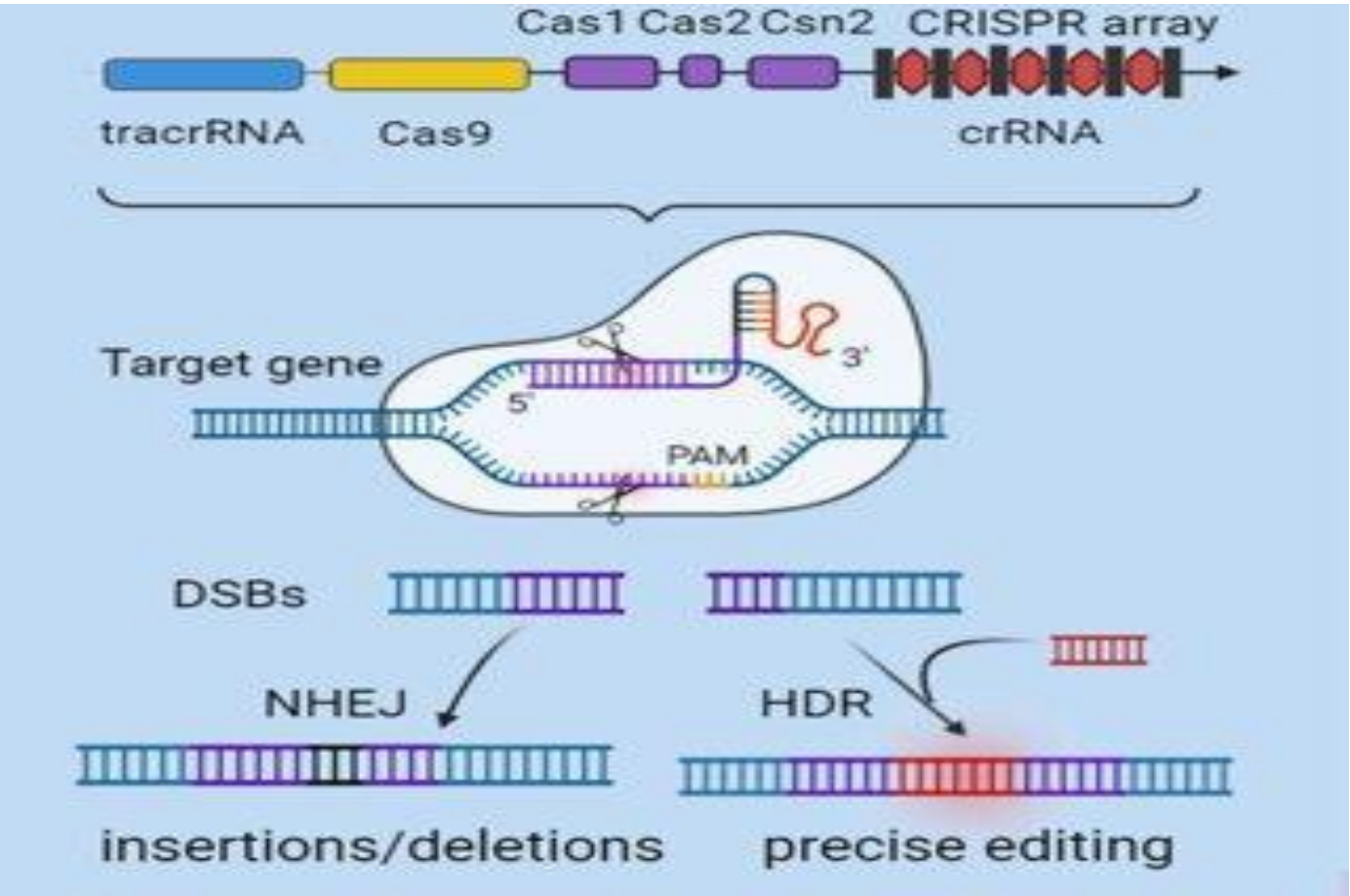
5.4.1. CRISPR/Cas9 in cervical cancer

To knock out a particular gene of interest, CRISPR/Cas9 generates specific DNA double-strand breaks (DSBs) using simple guide RNAs. (sgRNA). This is achieved by the Cas9 nuclease after the DNA break is repaired by non-homologous end joining . Preclinical studies and Clinical studies have shown the advantages and disadvantages of the delivery mechanisms used for this therapy, such as viral mechanisms, especially adenovirus. And lentiviruses, and non-viral mechanisms, e.g. electroporation, microinjection and lipid-based nanoparticles. Advantages of viral administration They involve high levels of transgene transduction and expression, but limitations include immunogenicity, the risk of cancer development, and the introduction of limited sequence. Other obstacles to viral delivery include off-target effects and guided RNA (gRNA) nuclease degradation . Compared to viral delivery, the mechanisms of non-viral delivery are better understood Target gene and better dose control, but they are technically more difficult and therefore require extensive optimization, and the use of these mechanisms in vivo is more difficult.Zhen et al. (2014) studied the use of the CRISPR/Cas9 system for this Eliminate HPV E6 and E7 in cervical cancer cells and achieved efficient deletion of both genes and increased expression of tumor suppressors p53 and p21..

Furthermore, nude mice injected subcutaneously with cervical cancer cells and treated with the CRISPR/Cas9 system targeting E6 and E7 showed reduced tumor growth and increased tumor cell apoptosis .Another study conducted by Hu et al. (2014) found that targeting HPV E7 by CRISPR/Cas9 in cervical cancer cells Resulted in a down-regulation of E7 expression and a subsequent up-regulation of pRb .A more recent study also examined the effect of CRISPR/Cas9 against HPV E6 in HPV-18-positive human cervical cancer cell lines. The authors reported a significant decrease in E6, increase in p53 and induction of apoptosis in tumor cells.

Importantly, tumor growth was suppressed in a dose-dependent manner in nude mice injected with these cervical cancer cells and treated with CRISPR/Cas9 .

5.4.2. RNA interference (RNAi) in cervical cancer



RNAi using short hairpin RNA (shRNA) is a genetic engineering method that stably inhibits the expression of The target gene for relatively long periods of time . Satu etc. (2018) transduced human cervical cancer cell lines with an adeno-associated virus (AAV) vector containing shRNA targeting HPV-16 E6/E7 and found a significant decrease in E6 and E7 mRNA levels. In all cell lines tested, this was accompanied by an increase in the expression of p53, p21 and pRb, and apoptosis was induced in a concentration-dependent manner . Furthermore, in vivo xenograft models using mice transduced with this E6/E7-targeted shRNA showed a significantly reduced tumor volume without macroscopic changes such as edema, inflammation or body weight .The results of the above genetic approaches targeting HPV E6 and E7 Revealed promising therapeutic strategies for cervical cancer.

6. Conclusions

Cervical cancer represents a significant global burden and remains a serious treatment challenge, especially in low- and middle-income countries, where resources are limited and current treatment options are often unaffordable and inaccessible. It is therefore essential that all countries adopt the resolution adopted by the World Health Assembly in 2020 that calls for the “elimination of cervical cancer” by 2030, achieving the following three goals:

(1) HPV vaccination 90% of girls before age. Of 15
(2) screening 70% of women at 35 and after 45 years with high-yield tests and
(3) treating 90% of precancerous lesions and managing 90% of invasive cancer cases .

In addition, current treatment options for cervical cancer are associated with disabling side effects and tumor drug resistance. Despite significant progress in the use of combination therapies to improve the efficacy of single-agent treatments, new and improved therapies for the treatment of cervical

cancer are still urgently needed. Examples of alternative therapies that have been explored in cervical cancer include immunotherapy, targeted therapy and genetic approaches such as CRISPR/Cas9 and RNAi. Although these therapies are increasingly promising in terms of therapeutic results, many of them remain experimental and represent expensive alternatives. One approach that may lead to rapid and cost-effective drugs is to identify commercially available cancer-free drugs that target host factors that cooperate with the HPV oncoproteins, particularly E6 and E7, which drive the progression of the cervical cancer. This strategy, which combines a targeted approach with the repurposing of drugs, is interesting because, compared to conventional anti-cancer therapies, it should allow identifying more effective drugs with lower side effects. Are significantly reduced and, as their safety profiles are known, they should be rapidly implemented in clinical trials.

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