Therapies and nanotherapies for cervical cancer (Review)

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Abstract. Cervical cancer (CC) is a major global health concern, ranking fourth worldwide in mortality, due to its high death rate and strong link to persistent high-risk human papillomavirus infections, which drive cancer progression through cellular dysregulation. Conventional therapies used in the treatment of CC have significant disadvantages, such as adverse side effects that affect the quality of life of patients. These side effects may include nausea, vomiting, fatigue, hair loss, fertility problems, damage to nearby organs and systemic toxicity. To address these challenges, there has been an increased interest in using nanotechnology to improve CC therapy. Nanotechnology enables the targeted delivery of drugs or therapeutic agents directly to tumor cells, improving the bioavailability and stability of the treatment. In addition, nanomolecules can overcome biological barriers to ensure precise delivery of drugs to targeted tissues. Currently, several delivery nanosystems enable the transport of drugs to their target sites without altering their composition and preventing them from being degraded. Extensive research has demonstrated the benefits of applying nanotechnology in targeted therapies for different cancer types, seeking to overcome the limitations of conventional therapies and allowing more precise and effective administration of treatments. Therefore, the present review highlights promising nanoparticles used to specifically target CC cells, aiming to enhance the effectiveness of treatment and reduce side effects, thus improving the quality of life of patients.

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1. Introduction

Cervical cancer (CC) is the fourth leading cause of mortality in women, claiming 341,831 lives worldwide, and is one of the main types of cancer affecting women of all ages, with an incidence rate of 604,127 new cases reported in 2020, according to the International Cancer Genome Atlas (IARC) (1). CC is associated with the persistent infection of high-risk human papillomaviruses (HR-HPV), where the expression of its oncoproteins E6 and E7 promotes the dysregulation of cellular processes characteristically altered in cancer (2). E7 mediates the degradation of numerous cellular proteins, including the retinoblastoma protein (pRB). The direct interaction of E7 with pRB promotes its degradation. pRB is a crucial regulator of the cell cycle, and its degradation results in the loss of proliferation control (3). Hyperproliferation induced by E7 would cause cellular mechanisms to initiate controlled cell death; however, the virus evades this response by expressing E6. E6 induces the degradation of p53, a key regulator of apoptosis mechanisms, and p53 degradation inhibits apoptosis mechanisms leading to cellular immortalization (4,5). Moreover, the coordinated expression of these proteins dysregulates angiogenesis and promotes invasion and metastasis, as well as the decrease in telomerase activity and the decrease in the activity of growth suppressors related to carcinogenesis (6).

To date, there are prophylactic alternatives to prevent infections of at least nine types of HR-HPV (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) (7). These alternatives have shown positive effects on prevention, but it is unclear if these prophylactic alternatives improve an already established infection. For this reason, inhibition of specific molecules, such as E6 and E7, could precisely enhance CC therapies (8). Moreover, drugs administered in CC therapy that aim to inhibit pathways related to carcinogenesis have shown positive effects in CC treatment. However, their high degree of cytotoxicity has also been documented (9). To address this, an enhanced approach based on the molecular insights of viral pathogenesis could be instrumental in developing more effective prevention and treatment strategies for CC (10-12).

There have been significant advancements in CC treatment, for which various approaches are available. These include surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapies. Notably, these conventional treatments are highly invasive, toxic, and cause numerous side effects, including leukopenia, thrombocytopenia, gastrointestinal damage, metabolic alterations, and drug resistance, which makes it challenging to ensure both the quality of life and treatment survival of patients. For these reasons, it is crucial to prioritize the development of targeted and personalized therapies that minimize cytotoxicity and reduce adverse effects (13,14). For instance, it is possible to develop multimodal treatment approaches that combine conventional therapies and nanotechnologies to improve effectiveness in treating CC and reducing side effects. The lack of effective treatments and their complications have spurred the development of nanosystems, which offer promising advancements in improving cancer therapies. Nanosystems engineered at the molecular level have shown great potential in revolutionizing cancer treatments, addressing the limitations of conventional approaches, and enhancing effectiveness while minimizing side effects (15).

Nanotechnology, a branch of technology that manipulates and controls matter at the nanoscale, holds immense potential for various industrial and biomedical applications. At the heart of nanotechnology are nanoparticles, nano-objects with 3D external dimensions at the nanoscale. These nanoparticles, including nanobars and nanoplates, enable groundbreaking advancements in diverse fields driven by scientific knowledge and innovation (16). The aim of the present review was to provide a comprehensive understanding of the differences between conventional and next-generation nanosystem-based treatments for CC. Through a detailed analysis, the importance of developing innovative therapeutic strategies based on nanotechnologies that can improve treatment outcomes, overcome the limitations of traditional approaches, and reduce side effects is highlighted. Thus, the present review focuses on showing how nanosystems offer transformative potential in the treatment of CC, overcoming the barriers of conventional therapies.

2. Conventional treatments used in CC

Cervical intraepithelial neoplasia (CIN), closely associated with HR-HPV infection, can progress to either *in situ* or invasive carcinoma (17). CIN is classified into three grades: CIN 1 (low-grade), CIN 2 (moderate), and CIN 3 (severe) (18). The invasive stage of CC is correlated with a poor prognosis and entails the spread of cancer cells to adjacent structures. Although CIN staging pertains to the precancerous condition, invasive CC is staged using the FIGO classification, which divides the disease into stages I-IV (19). In stage I, carcinoma is strictly confined to the cervix and subdivided into invasive carcinoma IA which can only be diagnosed by microscopy (IA1 and IA2), and invasive carcinoma IB (IB1, IB2, and IB3) with invasion ≥5 mm, limited to the uterine cervix. In stage II, subdivided into IIA (IIA1 and IIA2), the carcinoma invades beyond the uterus, without affecting the lower third of the vagina and the pelvic wall, limited to two-thirds of the vagina, while in IIB there is parametrial involvement but not reaching the pelvic wall. In stage III, subdivided into IIIA, IIIB, and IIIC (IIIC1 and IIIC2), the carcinoma affects the lower third of the vagina. In this stage the carcinoma invades the pelvic wall causing hydronephrosis, involving pelvic and para-aortic lymph nodes. In stage IV, the carcinoma has spread beyond the pelvis affecting the bladder or rectum (20).

First-line treatment options include surgery, radiotherapy, and chemotherapy (Table I). The International Federation of Gynecology and Obstetrics (FIGO) recommends surgery as immediate early-stage treatment (IA, IB1, IB2, and IIA1), and in cases with contraindications for surgery or anesthesia, radiotherapy is the suggested alternative. However, in advanced stages (IB3, IIA2, IIB-IVB), platinum-based chemotherapy combined with external radiation and intracavitary brachytherapy is recommended. Additionally, the application of radiotherapy and chemotherapy, in combination, is recommended (20,21). Nevertheless, second-generation therapy administration is necessary for patients with unsatisfactory responses to first-generation treatment or disease recurrence. These therapies involve a combination of drugs that collectively enhance the treatment response. Treatment of both precursor lesions and cancer is highly invasive, causing numerous side effects that negatively impact the quality of life of patients (22).

To enhance the treatment response of patients, combined alternatives such as immunotherapy, hormonal therapy, stem cell transplantation, and targeted therapy have been proposed (23). One of the challenges in cancer treatment is the occurrence of side effects that can potentially harm healthy tissues or organs. However, advancements in targeted cell therapy serve as the cornerstone of precision medicine, revolutionizing cancer treatment by employing macromolecular drugs or monoclonal antibodies targeting intracellular markers. This approach offers immense potential for personalized and effective cancer management (24). However, these therapeutic strategies often face significant limitations, including low aqueous solubility, systemic cytotoxicity, rapid degradation at the physiological level, and poor gastrointestinal absorption. To improve these promising therapies, attention has shifted to the design of efficient drug delivery systems. While conventional approaches have shown some utility, they have fallen short in effectively delivering a wide range of drugs (25).

3. Chemotherapy in the treatment of CC

Cisplatin, 5-fluorouracil, and pembrolizumab are drugs widely recognized as first-line treatments for patients with CC, as

Table I. Therapies used in the different stages of cervical cancer.

Stage	Treatment
IA1	• Surgical conization. • Total hysterectomy • Pelvic lymphadenectomy
IA2	• Pelvic lymphadenectomy • Radical hysterectomy with removal of lymph nodes • Radical uterine cervicectomy
IB	• Radical hysterectomy • Pelvic lymphadenectomy • Radical trachelectomy
IB2 and IIA1	• Surgery or radiotherapy • Radical hysterectomy and removal of pelvic lymph nodes along with chemotherapy (cisplatin or carboplatin)
IB3 and IIA2	• Pelvic irradiation • Platinum-based chemoradiation
IVA	• Pelvic exenteration • Radiotherapy
IVB	• Radiotherapy • Chemotherapy (bevacizumab, cisplatin, ifosfamide, irinotecan, gemcitabine, paclitaxel and topotecan), can be administered alone or in combination
Recurrence	• Radiotherapy combined with immunotherapy (pembrolizumab) and/or chemotherapy such as cisplatin, carboplatin, ifosfamide, irinotecan, gemcitabine, paclitaxel, topotecan and vinorelbine • Pelvic exenteration

Adapted from Refs (67-69).

they are fundamental for the effective management of the disease in its initial phase (22,26). However, in patients at stage IB2 and beyond, based on the FIGO classification, treatment primarily relies on the administration of cisplatin, as it is the most extensively studied and active agent. In patients where the administration of these drugs does not offer optimal results, the combined use of cisplatin and topotecan has shown promising results as a second-line therapy for patients with advanced, recurrent, and persistent CC (27). In addition, other research has been conducted on multi-drug combination alternatives to improve response to CC, such as the combination of paclitaxel, carboplatin, and bevacizumab, which is safe and effective in cases of advanced or recurrent CC (28). Scatchard *et al* (29) in 2012, demonstrated that cisplatin-based regimens are the most widely used, due to their high response rate and low toxicity compared to regimens in combination with cisplatin and nonplatinum regimens. Various drugs used in different types of cancer is shown in Table II.

As an alternative to standard chemotherapy, oncologists recommend the use of novel drugs such as pazopanib (an antiproliferative and anti-angiogenic drug), lapatinib and temsirolimus (antiproliferative drugs) (30). However, there are significant side effects associated with the administration of these drugs individually or in combination (Fig. 1) (31). Lapatinib is a tyrosine kinase inhibitor that targets and inhibits the human epidermal growth factor receptor type II and epidermal growth factor receptor (EGFR), thereby decreasing cell proliferation and cell migration (32). Furthermore, temsirolimus exerts its antitumor activity primarily through selective inhibition of the mTOR pathway, altering multiple cellular processes involved in tumor progression and angiogenesis (33). Moreover, pazopanib inhibits several growth factors such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and EGFR. By blocking these signaling pathways, which enhance the growth and survival of tumor cells, pazopanib can help slow cancer progression (Fig. 1) (34,35). Similarly, chemotherapeutic drugs such as cisplatin and topotecan affect cell growth and induce an antiproliferative effect on tumor cells; both approaches, inhibiting growth factors and inducing antiproliferative effects, represent complementary strategies in cancer treatment by interfering with key mechanisms that tumor cells rely on for growth and survival (24,25). Cisplatin has no net charge and is not subject to the Born energy barrier, which prevents small hydrophilic ions from diffusing through the lipid phase of cell membranes; its internalization into tumor cells occurs through passive diffusion across the cell lipid membrane, rendering it one of the most used chemotherapeutic agents for CC treatment (Fig. 1) (33). Moreover, in patients with advanced, recurrent, and/or persistent CC, oncologists recommend the use of combinations of paclitaxel (cell inhibitor), carboplatin (cell proliferation and division inhibitor), and bevacizumab (anti-angiogenic inhibitor) (26).

Although chemotherapy is widely used, Scatchard *et al* reported that various studies involving patients with CC have linked chemotherapy to serious adverse outcomes, including deaths related to neutropenic sepsis, severe thrombocytopenia, pulmonary toxicity, encephalopathies, sudden cardiac death,

Table II. Summary of the types of drugs administered for various types of cancer.

Type of drug	Function	Drugs	Type of cancer
Alkylating agents	Inhibition of DNA replication and transcription	Nitrogen mustard: Bendamustine, cyclophosphamide and ifosfamide Nitrosoureas: Carmustine and lomustine Platinum analogs: Carboplatin, cisplatin and oxaliplatin Triazenes: Dacarbazine, procarbazine and temozolamide Alkyl sulfonate: Busulfan Ethyleneimine: Thiotepa	Lung, breast and ovarian cancer, as well as leukemia, lymphoma, Hodgkin lymphoma, multiple myeloma and sarcoma.
Antimetabolites	Inhibition of DNA replication	Cytidine analogs: Azacitidine, decitabine, cytarabine and gemcitabine Folate antagonists: Methotrexate and pemetrexed Purine analogs: Cladribine, clofarabine and nelarabine Pyrimidine analogs: 5-FU, and capecitabine (prodrug of 5-FU)	Leukemias, breast, ovarian, pancreatic and bladder cancer, as well as sarcoma, Hodgkin lymphoma, colorectal, anal and gastric cancer.
Antimicrotubule agents	Inhibit RNA and DNA synthesis and disruption of the balance of microtubule polymerization and depolymerization	Topoisomerase II inhibitors: Anthracyclines Topoisomerase I inhibitors: Irinotecan and topotecan Taxanes: Paclitaxel, docetaxel, cabazitaxel Vinca alkaloids: Vinblastine, vincristine, vinorelbine	ALL, AML, Wilms tumor, neuroblastoma, sarcomas, breast, ovarian, bladder and thyroid cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, as well as colorectal, cervical, esophageal pancreatic, lung and prostate cancer.
Antitumor antibiotic	Inhibits DNA and RNA synthesis	Actinomycin D, bleomycin, daunomycina	Testicular, Hodgkin lymphoma, as well as head, and neck cancers.
Others	Inhibit ribonucleoside diphosphate reductase; S-phase specific; induces cell differentiation	Hydroxyurea, tretinoin, arsenic trioxide and proteasome inhibitors	Leukemias

Adapted from Refs (20,73,74). DNA, deoxyribonucleic acid; RNA, Ribonucleic acid; 5-FU, fluorouracil; ALL, acute lymphoblastic leukemia; AML, Acute myeloid leukemia.

and cerebrovascular accidents (29). Therefore, significant interest has been placed in developing novel alternatives to reduce the effects caused by chemotherapy, thereby improving the survival outcomes of patients with CC.

4. Nucleic acid-based therapy

In recent years, RNA molecular biology has undergone revolutionary advances that have led to a profound understanding of the mechanisms of gene regulation (36,37). The identification and characterization of small non-coding RNAs was a groundbreaking discovery. Small non-coding RNAs are molecules composed of 20-30 nucleotides that play an essential role in the post-transcriptional modulation of genes and genomes (34). This breakthrough has paved the way for the advancement of nucleic acid-based therapies utilizing DNA or RNA molecules to target genes associated with pathological processes. These therapies encompass various approaches, including plasmid DNA, small interfering RNA, and microRNAs (pDNA, siRNA, and miRNAs, respectively) (35).

Owing to their marked sensitivity and specificity, siRNAs have emerged as promising therapeutic agents that can potentially replace or complement traditional chemotherapy approaches (37,38). Targeted siRNAs, often considered for cancer therapy, include genes that promote uncontrolled cell growth, such as VEGFs, c-Myc, EphA2, Raf-1, Plk1, CDKs, survivin, and multi-drug resistance genes, to mention a few, that help cancer cells survive or resist chemotherapy (39-44) Aberrant expression or activity of these genes causes cells to escape from well-controlled cell cycles, resulting in malignant transformation, which involves alterations in cytoskeletal modulation, cell migration, proliferation,

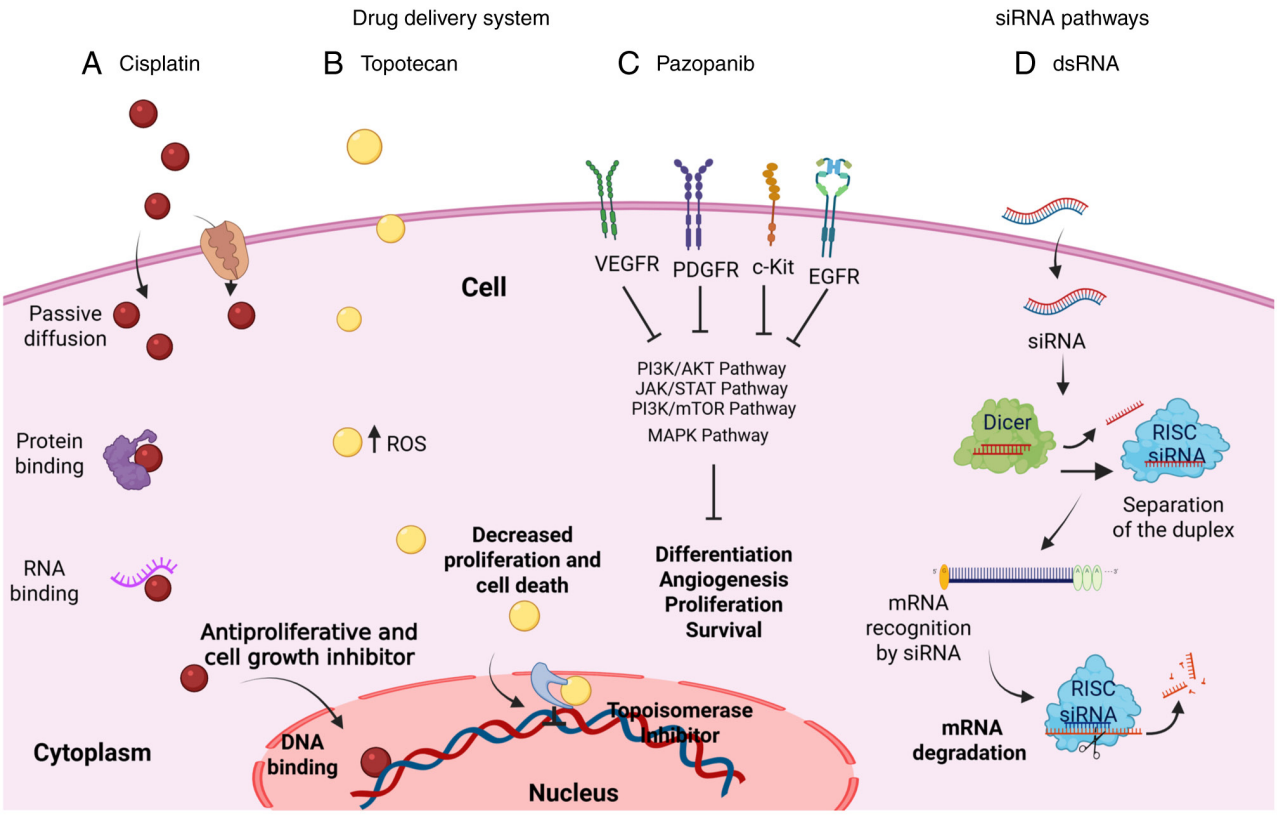

Figure 1. Drug-based therapies and genetic silencers. This image illustrates the effects of various drugs and genetic silencers used in cervical cancer therapy, including (A) cisplatin, (B) topotecan, (C) pazopanib and (D) dsRNA. These agents act by inhibiting processes such as cell proliferation, differentiation, and angiogenesis, while promoting cell death. In the image, activation is represented by arrowheads, whereas inhibition or blockade is indicated by transverse lines. dsRNA, double-stranded RNA; ROS, reactive oxygen species; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; siRNA, small interfering RNA; RISC, RNA-induced silencing complex. The figure was created using BioRender software (https://biorender.com/).

and angiogenesis, among others (45,46) However, nucleic acid-based therapy is hindered by several disadvantages, including intrinsic molecule degradation by cellular nucleases and low cellular uptake (38). These challenges have been effectively addressed through various strategies, including the chemical modification of siRNAs and the utilization of nanoparticle delivery systems based on lipids, polymers, and inorganic platforms. These approaches serve the dual purpose of protecting RNA molecules from cellular nucleases and facilitating their efficient uptake by target cells (46).

5. Nanoparticles: An alternative for the treatment of CC

Nanoparticles are an important class of nanosystems used for medical applications. These systems consist of nanoparticles of different sizes and shapes that are capable of binding, encapsulating and/or transporting one or more active substances, including small molecules, proteins, and nucleic acids; their small size allows them to be administered both systemically and locally, with efficient cellular internalization and diffusion (Fig. 2A) (37).

Nanotechnology-based delivery systems include viral systems such as retroviruses and adenoviruses, among other viral types (47), and nonviral systems: Biodegradable nanoparticles, dendrimers, polymeric micelles, liposomes, microcapsules, solid lipid nanoparticles (SLNs), and solid nanoparticles (48). Polymers and liposomes of cationic nature are among the most widely used nanocarriers for the delivery of genetic material in cancer therapy (Fig. 2A) (49). Engineered nanosystems have been developped to carry gene-silencing molecules such as E6/E7 siRNA and Derlin1-siRNA, which inhibit specific signaling pathways including PI3K/AKT, JAK/STAT, PI3K/mTOR, and MAPK, as shown in Fig. 1 (50,51). However, most treatments based on the use of siRNAs are in experimental (preclinical) phases. By contrast, targeted therapy drugs, such as Doxil®, Abraxane®, Lipoplatin® are in advanced clinical stages (52). The formulations of these nanosystems improve CC therapy and enhance the efficiency of drug delivery for agents such as cisplatin, topotecan, and pazopanib, along with their mechanism of action against dsRNA (Fig. 1).

The use of nanoparticles in cancer treatment overcomes the limitations of conventional chemotherapy by enhancing the precision and efficacy of therapy. In addition, the use of nanoparticles can monitor disease progression and adapt to specific tumor microenvironment conditions, such as hypoxia and acidity, optimizing drug absorption and concentration within tumor tissue (53). Due to their biocompatibility, permeability, and retention properties, nanoparticles serve as efficient drug carriers, allowing for a reduction in both dosage and treatment frequency, thereby minimizing toxicity. Furthermore, the development of stimulus-responsive systems has improved

Table III. Comparison of the various types of nanoparticle-based therapies.

Nanocarriers	Advantages	Disadvantages/limitations
Lipid systems	-Enhancing oral absorption	-Drug leakage during storage
	-Eco-friendly degradation	-Restricted loading capacity for water-soluble drugs
	-Compatibility with biological systems	-Changes in crystalline structure
	-Efficient encapsulation capacity	-Increase in particle size over storage duration
	-Superior structural stability	-Gelation of lipid-based dispersions
Polymeric systems	-High transfection efficiency	-Hydrophobicity
	-Biocompatibility	-Slow degradation
	-Biodegradable	-Existence of cytotoxicity
	-Low toxicity	-Lack of functional groups
	-Efficient mechanical properties	
	-High elasticity	
Inorganic systems	-Large surface area relative to volume	-Adverse effects on biological systems
	-Enhanced structural stability	-Limited permeability
	-Easily customizable surface properties	-Unclear correlation between particle size and toxicity
	-Compatibility with biological systems	
	-Porous architecture for efficient functionality	
	-No reaction with drugs	
	-Excellent biocompatibility with minimal toxicity	

Adapted from Refs (56,75-77).

controlled drug release, and certain nanoparticles can function as specific markers to direct therapy precisely to cancer cells (54).

Currently, the nanoparticles used in CC treatment have several limitations (Table III). For instance, lipid-based nanocarriers exhibit low cellular internalization, are prone to the accelerated blood clearance phenomenon, can cause hemolysis, and present challenges in achieving industrial-scale production. Polymeric nanoparticles face limitations such as low drug loading capacity and potential cytotoxicity. In the case of inorganic nanomaterials, the main drawbacks include toxic effects on biological systems, low permeability, and uncertainties regarding the relationship between particle size and toxicity (55). Furthermore, most nanoparticles are costly and complex to produce since their synthesis requires expensive technologies. In addition, there is a lack of preclinical studies, and their application in humans remains limited. This is due to the need to evaluate their safety and effectiveness in the long term before regulatory approval can be granted (56). However, despite all these challenges, nanoparticles are a promising option in the fight against CC, provided these limitations can be overcome.

6. Lipid systems in conventional therapy

Liposomes are lipid-based spherical vesicles composed of phospholipids that form a lipid bilayer surrounding an aqueous core (57). Liposomes are composed of natural or synthetic compounds, and their constituents are not exclusive to lipids since new-generation liposomes can also be formed from polymers (occasionally referred to as polymeromas); some of the main characteristics of liposomes are that they are biocompatible and biodegradable. In addition, they can compartmentalize and solubilize in both hydrophilic and hydrophobic media. These characteristics render them effective transport vehicles for drug delivery (58).

Among the lipid-based systems for drug delivery, lipid nanoparticles based on hydrogenated soybean L-α-phosphatidylcholine (HSPC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000] (DSPE-mPEG$_{2000}$), and cholesterol loaded with cisplatin and mifepristone (L-Cis/MF) have been developed (Fig. 2A and B). In *in vitro* experiments, these nanoparticles have exhibited cytotoxic effects on CC cells. Moreover, when tested *in vivo*, these nanoparticles have decreased tumor growth, demonstrating that this lipid system loaded with L-Cis/MF enhances the effect of chemotherapy (59). Cationic liposomes are not an appropriate delivery system in *in vivo* models because, when injected systemically, they are quickly degraded from the bloodstream, which limits their ability to reach their target site. For this reason, incorporating a flexible polymer such as PEG into liposomes can significantly prolong circulation time (60).

Liu *et al*, developed an SNL loaded with both paclitaxel and TOS-cisplatin and marked it with a signal peptide (TAT) to specifically target the nanoparticles to CC cells. They demonstrated that these nanoparticles exhibited enhanced cytotoxicity against CC cells compared with the individual drug formulations alone. Co-administration of both drugs using the nanoparticles resulted in cell growth inhibition, induction of programmed cell death, and increased antitumor efficacy in mouse models of CC (61). These findings suggest that this formulation strategy could improve conventional therapy in the treatment of CC (62).

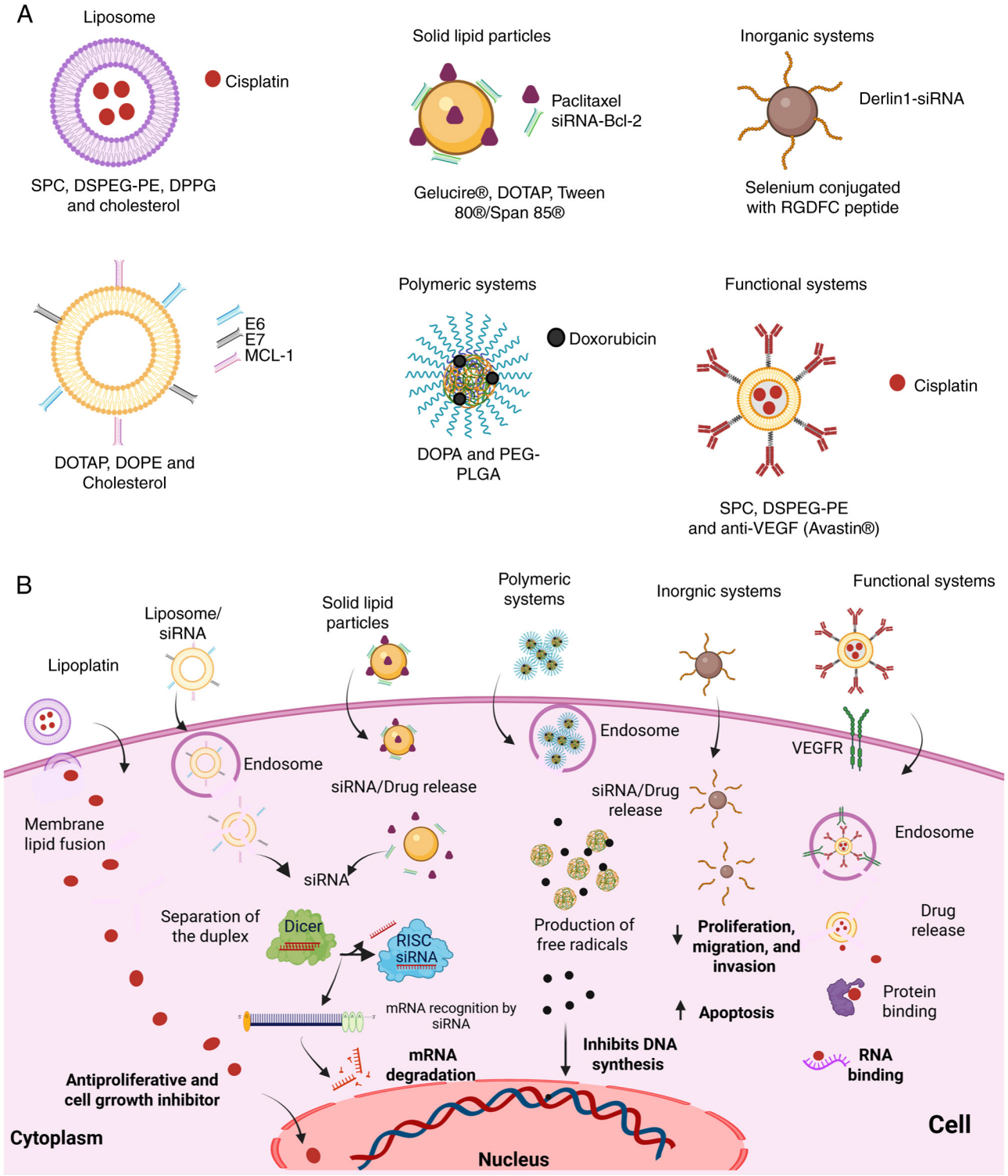

Figure 2. Delivery systems for drugs and gene silencers. (A) Schematic representation of delivery systems used in drug delivery and gene silencers. (B) Mechanism of action of various drug delivery systems and gene silencers. DOPA, dioleoylphosphatidic acid; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DOTAP, 1,2-dioleoyl-3-trimethylammonium propane; DPPG, 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol; DSPEG-PE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000]; HSPC, hydrogenated soybean L-α-phosphatidylcholine; PEG-PLGA polyethylene glycol-polylactic acid-co-glycolic acid; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; SPC, soya phosphatidylcholine. The figure was created using BioRender software (https://biorender.com/).

7. Advances in targeted therapy with lipid-based systems

A propensity for nuclease-mediated degradation and their low cellular uptake are the disadvantages of targeted nucleic acid therapies (38). These challenges have been addressed in several ways, including the chemical modification of siRNA molecules. In addition, nanoparticle delivery systems based on lipids, polymers, and inorganic platforms, have been implemented to protect RNAs from cellular nucleases and facilitate the passage through target cell membranes (46).

The lipid-based therapy systems have led to significant advancements, particularly in the local vaginal administration of siRNAs for the treatment of CC (Fig. 2A). A notable study conducted by Lechanteur *et al* (63), demonstrated the efficacy of liposomes designed with a composition of 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) as a cationic lipid, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), cholesterol, and ceramide-PEG_{2000} coupled with a mixture of E6, E7, and MCL-1 siRNAs. These liposomes targeted the oncoproteins associated with HPV 16 and HPV 18 carcinogenesis, confirming successful silencing of these oncoproteins in cell lines positive for the respective HPV types (Fig. 2B). The coating of lipoplexes with 20% ceramide-PEG_{2000} has emerged as a significant advancement in siRNA delivery, particularly for HPV-positive cells. This coating enables the efficient release of active siRNA into the cytoplasm of the cell, leading to desirable biological responses. Furthermore, the inclusion of PEG prevents the aggregation of mucin proteins within lipoplexes, ensuring that their size remains at ~200 nm (64). Similarly, DOTAP-based lipoplexes with PEG_{2000}, loaded with E6 siRNA (Lipoplexes-PEG-HPV16 E6), significantly reduced HPV16 E6 protein levels. By contrast, p53 protein expression was restored, resulting in the inhibition of carcinogenic processes such as proliferation, migration, and cell invasion in CaSki cells. This demonstrates that this system is a viable option to complement CC treatment (38).

Another alternative to improve conventional CC treatment has been the development of therapies based on the use of siRNAs (Fig. 2A), such as the development of vaginal suppositories based on SLNs composed of Gelucire®, DOTAP, Tween 80®/Span 85® loaded with paclitaxel, siRNA-Bcl-2, and paclitaxel/siRNA-Bcl-2 (Fig. 2B). In addition, researchers demonstrated that SLNs loaded with Bcl-2 siRNA have higher toxicity at lower doses than SLNs loaded with paclitaxel alone. Additionally, SNLs loaded with Bcl-2 siRNA/paclitaxel provided greater apoptosis of paclitaxel-resistant cells, with advantages such as a reduction in the paclitaxel dose entering the systemic circulation, cytotoxic reduction, protection of enzymes present in serum and the possibility of being self-administered without professional assistance (65).

Javadi *et al*, presented a compelling strategy to treat CC by utilizing E6/E7 siRNAs transfected with Lipofectamine® RNAiMAX (66). This approach successfully led to decreased cell viability and increased apoptosis in CC cell lines. Additionally, the study evaluated the synergistic effect of combining these siRNAs with anti-miR-182. This combination resulted in a significant increase in apoptosis and a reduction in cell viability. The combined action of these agents suggests their potential as promising therapeutic candidates for CC treatment. Finally, they evaluated the simultaneous use of cisplatin and E6/E7 siRNAs and demonstrated that cell viability was dramatically lower in CaSki cells than in those treated with cisplatin alone (66). Similarly, it has been documented that the use of lipid-based systems coupled with HPV16 E6-siRNA targeting the E6 oncoprotein of HPV 16 significantly decreased the expression of the E6 oncoprotein and restored the expression of the p53 protein, leading to a significant reduction in migration and invasion in CC-positive cells (38). This demonstrates that lipid-based systems could be considered a viable therapy option.

8. Enhanced therapeutic approaches with polymeric systems

Advancements in medical treatments have increasingly turned to polymeric systems to enhance therapeutic efficacy. These systems, composed of natural, synthetic, or semisynthetic polymers, offer unique advantages such as improved biocompatibility and biodegradability (67). Among natural polymers, hyaluronan, albumin, gelatin, alginate, collagen, and chitosan have been experimentally tested, and among synthetic polymers, PEG, polylactic acid (PLA), and polyglycolic acid (PGA) are mentioned in literature as potential carriers. Occasionally PLA and PGA are used as copolymers (PLGA) (68,69). Polymeric-based system, PLGA, has regained significant interest since it is a biodegradable polymer that has been used as a vehicle for drug delivery since its approval by the FDA as a copolymer (39). These polymeric systems enhance the stability and control the release of therapeutic agents while minimizing adverse effects, thereby paving the way for more effective and safer medical interventions.

In 2020, Xu *et al* (70), developed a PLGA-based nanosystem (si/PNPs@HeLa) to improve CC therapy. Using this system, they encapsulated paclitaxel and an HPV18 siRNA-E7, which was subsequently coated with a HeLa cell membrane to mimic the membranes of the target cells. The utilization of HeLa cell membranes not only enhanced the selectivity of the nanosystem but also inhibited the immune response, resulting in improved specificity of delivery to the target tissue, suggesting that E7 siRNA could improve paclitaxel-induced resistance by inhibiting the activation of the AKT pathway; thus, the synergistic effect between paclitaxel and E7 siRNA resulted in an improved CC remission and suppression in an *in vivo* model (70).

The development of novel drug delivery systems for cancer treatment represents an opportunity to evaluate the synergistic effect of different medications, with the potential to create particles that allow for the specific and efficient delivery of multiple drugs. Accordingly, nanoparticles based on dioleoylphosphatidic acid (DOPA) and PEG-PLGA loaded with curcumin and SN38 have been developed and have demonstrated increased apoptosis in HeLa and A2780 cells (41), as well as antitumor effects in xenograft models of colorectal cancer (40). Another polymeric system that has demonstrated antitumor therapeutic potential due to its high cellular internalization capacity, easy release of doxorubicin, and low cytotoxicity is based on poly-γ-glutamic acid (γ-PGA) and cholesterol-NH2 (γ-PGA/Chol) particles loaded with Dox (Fig. 2A). These advancements underscore the promise of polymeric systems in revolutionizing cancer treatment by enabling targeted and efficient drug delivery, thereby enhancing therapeutic outcomes while minimizing side effects (Fig. 2B) (71).

9. Inorganic-based systems for CC therapy

Inorganic systems have demonstrated high efficiency for the transport and delivery of various molecules in cancer therapy. Inorganic nanoparticles are tiny particles that exhibit unique and enhanced physical and chemical properties depending on their size (42). Among inorganic materials, the use of mesoporous silica nanoparticles, graphene oxide, black phosphorus,

and gold nanoparticles is notable. Their advantages include high efficiency in drug loading and release, maintaining their structure intact in the bloodstream, and their biocompatibility (43,44). Building on these advantages, specific applications in CC therapy are being explored. For instance, selenium nanoparticles conjugated with both RGDfC peptide (which is highly expressed in cancer cells) and Derlin1-siRNA (Fig. 2A and B), resulting in RGDFC-Se@siRNA are being experimentally tested. This combination was revealed to suppress proliferation, migration and invasion, and promote the apoptosis of HeLa cells. In addition, this nanosystem was highly effective at inhibiting CC cells; thus, this alternative is a promising strategy for the treatment of CC (45).

Another novel drug delivery proposal is based on anionic clay-based systems [layered double hydroxide (LDH)]. The design of this system was based on the $Mg_{0.655}Al_{0.344}(OH)_2[(MTX)_{0.107}CL_{0.128}]\cdot 0.1H_2O$ for the delivery of methotrexate (LDH-MTX), which was assessed in an orthotopic CC model of C33A cells, and an antitumor effect was demonstrated; therefore, LDH-MTX has been proposed as a promising alternative in chemical treatment due to its low toxicity both *in vitro* and *in vivo* (46). To summarize, the advancement of inorganic systems for drug delivery marks substantial progress in CC therapy. These systems exhibit high efficacy in targeting and suppressing cancer cell growth, and the potential to minimize toxicity, making them promising candidates for future clinical applications.

10. Functional nanoparticle therapy

Other promising systems for admixing drugs and/or molecules are nanoparticle systems, which involve the conjugation of molecules on the surface of the nanoparticles (72). For instance, the optimization of arsenic trioxide encapsulated in folate-mediated liposomes has demonstrated enhanced efficacy in the *in vitro* treatment of HPV-positive CC cells. The results indicated that small-sized and negatively charged liposomes, along with the incorporation of folate as a specific targeting medium exhibit improved cell internalization capacity and more efficient release of arsenic trioxide into cancer cells. This enhances the selectivity of the treatment and augments the inhibitory effects on cell growth. However, further studies, including *in vivo* models, are necessary to validate and assess the feasibility of this approach in a real clinical setting (47,48). Organic-inorganic nanohybrid niosomes have been developed as another alternative for drug delivery in CC; for example, nanoparticles based on iron oxide, PGLA with PEG, folic acid and turmeric (F3O4@PGLA-PEG@FA/Cur) have been shown to increase the efficiency of cell internalization *in vitro* and increase the rate of apoptosis in CC cells, suggesting that folate-conjugated nanoparticles (niosomes) could be used to identify tumor cell surface receptors, thereby promoting drug bioavailability and improving the rate of tumor inhibition (49).

The search for novel and efficient drug alternatives for the treatment of cancer has allowed the search for natural extracts as therapeutic agents with the ability to inhibit the growth of cancer cells specifically but not normal cells; as an alternative, the use of monomyristin (MM), a monoacylglycerol found in saw palmetto, has been explored (50). Long-chain monoglyceride derivatives can induce programmed cell death in cancer cells. Changes in the expression of genes related to cell proliferation and survival have also been observed. The findings suggest that these compounds could have potential as therapeutic agents in the treatment of CC (51). However, due to their poor water solubility, functional nanoparticles based on PLA and hydrophobically modified dextrans, such as DexP26 or DexP26-COOH, which encapsulate MM coated with transferrin (Tf) ligands, have been developed for use in treating HeLa cells. These nanoparticles have shown a cytotoxic effect on HeLa cells that was enhanced by Tf conjugation, as it increases the efficiency and selectivity of MM treatment. These results suggest that this encapsulation strategy could hold promise for the development of more effective treatments for CC (52). Another system for the delivery of cisplatin involves the use of PLGA nanoparticles coated with a lipid layer based on soy phosphatidylcholine, DSPEG-PE and anti-VEGF (Avastin®) (L-PLGA-Cis-Avatin®) for enhanced specificity (Fig. 2A), allowing increased internalization of the particles *in vitro* and a decrease in cell viability; moreover, *in vivo*, this system results in greater accumulation in the tumor tissue and an inhibition of tumor growth, demonstrating that this nanosystem could improve the therapeutic efficacy of cisplatin by reducing its toxicity (Fig. 2B) (39).

The use of systems for the delivery of different molecules has enabled the drugs administered in conventional CC therapy to reduce nephrotoxicity at higher doses compared with the administration of free drugs such as Lipoplatin™ (57). These drug delivery systems have reduced adverse effects such as leukopenia, neutropenia, nausea, and asthenia in patients, providing a longer lifetime of the drug in circulation, and limiting toxicity in normal cells vs. the free administration of drugs (58,59). Similarly, the use of non-lipidic nanoparticles for drug delivery has been highlighted for its efficacy in inhibiting key cellular processes related to carcinogenesis, improving the penetration of the drug into the cellular interior, and considering this type of nanoparticle as an effective anticancer therapeutic agent (60,62). The various formulations described in the literature have been developed specifically according to the molecules to be transported (Fig. 2A and B); this specificity will allow the internalization of these molecules to inhibit key cellular processes in cervical carcinogenesis. This is the reason nanosystems have been considered as a potential targeted therapy against cancer (64). Regardless of their base formulation, this allows a variety of alternatives in cancer therapy to be considered to improve invasive treatments for patients.

11. Limitations of nanoparticle use in therapy

Nanoparticles have had a significant impact as alternatives in CC therapy; however, they face several limitations that restrict their use and efficiency. Among the main challenges are biocompatibility and toxicity risks, difficulties in large-scale production, stability and shelf-life issues, inefficiencies in drug delivery, and the precise targeting of therapies, all of which are addressed were addressed in the present review. Another noteworthy limitation is that most studies evaluating the effects of nanoparticles primarily focus on cellular and animal models, which restricts the understanding and comparison of their impact on humans. To overcome these limitations, it is

essential to increase the number of clinical studies, identify biodegradable materials with low or no toxicity, develop efficient and cost-effective production methods, enhance surface design to improve biocompatibility and responsiveness to external stimuli, and establish stricter regulatory protocols.

12. Conclusions and future perspectives

The use of and interest in nanotechnology has allowed the development of nanoscale systems for the transport of therapeutic agents in the area of medicine since most of the agents used in traditional therapy are severely aggressive and have several limitations both in terms of administration and assimilation, as well as in terms of performing their functions, which is the reason great interest has been placed in the design of novel delivery systems that can be efficient to improve the administration of molecules with specific targets.

One of the numerous advantages of these nanosystems is the high degree of control over their physicochemical characteristics, as well as the ability to transport various molecules such as drugs, genes or other substances, which allows them to be administered by various routes and safely internalized into the target cell. Although there is evidence of toxicity in some nanosystems, a good balance between this approach and the use of nanomaterials guarantees an effective transport system with low immunogenicity, greater safety, low toxicity, enhanced cargo, and greater specificity for the site of injury.

Future research directions in nanotechnology should focus on improving the biocompatibility of nanosystems and mitigating potential toxicities, especially in the long term. Additionally, strategies for targeted drug delivery should continue to be refined for complex diseases, such as cancer or neurological disorders, through approaches such as the use of specific ligands or receptors. Exploring novel nanomaterials with greater stability, lower immunogenicity, and enhanced delivery capabilities will be key to advancing nanotechnology-based therapies. Scalable and cost-effective manufacturing processes must also be developed to ensure widespread clinical application. Finally, research should explore the use of nanosystems in combination therapies to improve treatment efficacy. These research areas are essential for maximizing the potential of nanotechnology in enhancing drug delivery and clinical outcomes.

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Authors' contributions

LVSM and JAVD performed the literature research and preparation of tables. LVSM wrote the first draft and prepared the figures. CBR, YGG, MALV, LEAA, JON and BIA contributed to the writing, reviewing, and editing of the manuscript. JON and BIA supervised the study and acquired the funding. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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