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CURRENT ADVANCES IN NANOCARRIERS FOR CERVICAL CANCER

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ABSTRACT
Cervical cancer is the most second common malignant tumor occurring in women worldwide and it has a highest death rate, mainly when it is associated with human papilloma virus (HPV). In US, an approximately 12,820 cases of cervical cancer and an estimated 4,250 lives were taken by this cancer in the year 2017, by the conventional treatment the expected out comes are not occurred. Other approaches, such surgery, are frequently accompanied by risks that could affect subsequent pregnancies and deliveries, particularly in young female patients. one sees in the real need of new alternatives of therapy as the delivery of chemotherapeutic agents by nanocarriers using nanotechnology. This review discusses the many drug delivery methods used to treat cervical cancer. The main advantages of this drug delivery are improving pharmacological activity, bio availability, improvement of solubility, reducing the toxicity, by targeting of ligands, thus leads to create new therapeutic nanotechnologies in a too much needed area. The main disadvantage is the high cost of production of these nano carriers. In order to review the drug delivery methods based on nanotechnology used to treat cervical cancer, this review was covered.

KEYWORDS: cervical cancer; nanotechnology; nanocarriers; human papilloma virus; drug delivery strategies.

INTRODUCTION

A succession of mutations and modifications to the patterns of gene expression result in the transformation of healthy cells into abnormal cells during the complex, multistage process known as carcinogenesis. Inherited characteristics, environmental factors, food, and the risk of cancer rising with age are all factors that predispose to malignancy. Initiation, promotion, and progression are the three steps that make up the development of cancer, and ROS can affect each of these processes. Also, it is widely known that free radicals can damage DNA's bases and deoxyribose backbone by reacting with all of its components, which can result in the mutation of critical genes and ultimately cause cancer.

Cervical cancer

Cervical cancer affects the entrance part of the uterus (womb). The cervix is the smallest part of the lower uterus and it is often referred to as the neck of the womb. Almost all cervical cancers are caused by prolonging infection with one of the HPVs (Human Papillomavirus) Even though the HPV Infection is most common in people, but it does not develop cancer. Only a few of the more than 100 different HPV varieties have been associated with cancer. Benign warts on the skin or genitalia are brought on by other HPV strains. The supposedly "high risk" strains of HPV have been demonstrated to cause malignancies of the cervix and the penis in men. In both sexes, HPVs can also lead to malignancies of the mouth, throat, and anus. Sexual contact or skin-to-skin contact are the two main ways that HPV infection spreads.

Causes of Cervical Cancer

An infection with one of the high-risk HPV strains results in cervical cancer. Yet, since not everyone who has HPV will go on to develop cancer, it is likely that additional variables also contribute to the occurrence of cervical cancer. There are some known risk factors that raise a woman's chance of getting cervical cancer.

1. Tobacco smoking
2. HIV infection
3. Immune system suppression
4. Past or current Chlamydia infection
5. Overweight
6. Long-term use of oral contraceptives (although the risk returns to normal when the contraceptive pills are discontinued).
7. Having three or more full term pregnancies. Having a first full-term pregnancy before age 17.
8. Poverty.
9. Family history of cervical cancer

The most common Symptoms of the cancer are

- Bleeding between periods
- Bleeding after sexual intercourse
- Pelvic pain
- Smelly vaginal discharge Pelvic pain
- Vaginal discharge tinged with blood
- Bleeding in post-menopausal women Discomfort during sexual intercourse

Stages of development of the Cancer

Stage 0: Precancerous cells are present.

Stage 1; Cancer cells have grown from the surface into deeper tissues of the cervix, and possibly into the uterus and to nearby lymph nodes.

Stage 2; The cancer has spread through the cervix and uterus, but not yet to the pelvic walls or the lower vagina. It might or might not impact lymph nodes close by.

Stage 3; Cancer cells may be obstructing the ureters, the tubes that carry urine from the bladder, if they are seen in the lower portion of the vagina or the walls of the pelvis. Lymph nodes nearby may or may not be impacted.

Stage 4; The cancer, which spreads from the pelvis to the bladder or rectum, is malignant. The lymph nodes might or might not be impacted. It will eventually spread to distant organs in stage 4 like the lymph nodes, liver, bones, and lungs.

If any symptoms appear, it is crucial to get screened and to visit a doctor right once because prompt treatment improves survival rates.

Treatment for cervical cancer using nanotechnology

Nanocarriers

Nanomaterials are frequently used in the creation of new drugs, as drug carriers, and as tracers in the fields of medicine, biology, and life sciences. Nanomaterials have been demonstrated to be harmful to mammalian cells and to cause tumour cells to undergo apoptosis.

It was thought that nanoparticles produced a stronger biological reaction than microparticles, and that they may have an impact on cellular activity because of their smaller size, high number per mass, large specific surface area, and production of reactive oxygen species (ROS).

Zinc oxide nanoparticles in treatment of cervical cancer

According to multiple investigations, ZnO nanoparticles are more harmful to cells than ZnO microparticles in a variety of malignancies, including gliomas, breast, bone, colon, leukaemia, and lymphomas. When exposed to cells at increasing concentrations, the ZnO nanoparticle appeared to clearly demonstrate cytotoxicity against human cervical cancer cells. Effective separation of tumour and normal cells depends on the ZnO nanoparticle's differential cytotoxicity. At the low dosage utilised in this study, ZnO nanoparticle suppressed tumour cells, indicating that it may be effective as a possible anticancer treatment. The cytotoxicity and antioxidant potential of ZnO nanoparticle in the C2C12 and 3T3-L1 cells have been demonstrated in previous studies. According to Mariappan et al., ZnO nanoparticles are less hazardous to healthy peripheral blood mononuclear cells and inhibit human myeloblastic leukaemia cells. By using the SRB assay, ZnO nanoparticles clearly had a cytotoxic effect on HeLa cells. The treated cells exhibited the hallmarks of apoptosis, including cell rounding, random distribution, cell shrinkage, condensed and aggregated chromatin, the formation of apoptotic bodies, and compact granular masses. ZnO nanoparticles had a dynamic, concentration-dependent cytotoxic effect on HeLa cells.

Cytotoxic effect of TDZ (Thidiazuron) on human cervical cancer cells

TDZ was applied to normal and cervical carcinoma cells at varying doses (0.4-454 µM) At its highest concentration (454 µM), TDZ was found to be particularly efficient against cancer cells, inhibiting cell proliferation by up to 90%. Additionally, even at a lower concentration of TDZ 4.5 µM, the morphology of cancer cells was significantly affected. On the other hand, normal MDCK cells showed no effect from TDZ up to 45.4 µM of TDZ, and even cellular shape was unaffected. At 454 M of TDZ, it did, however, severely limit MDCK cell proliferation. The possibility that µM M of TDZ could be harmful to normal cell growth led to its exclusion from further research. The outcomes showed a dose-dependent pattern. At 0.4µM of TDZ concentration, there was no apoptosis. However, between 4.5µM and 45.4 µM of TDZ, there was a significant increase in the number of apoptotic cells. With the greater concentration of TDZ-treated cervical cancer cells, considerable DNA damage was seen.

Liposomes

After being discovered in 1965 by Bangham and his colleagues, liposomes quickly gained popularity as a medication delivery system Liposomes are closed, spherical vesicles made of cholesterol, synthetic dimyristoyl phosphatidylcholine (semisynthetic DMPC), natural phospholipids (egg yolk lecithin and soybean lecithin), and a central aqueous cavity. Numerous phospholipids and excipients may be used to create liposomes, creating flexible systems that are simple to modify in the formulation. Thus, a variety of techniques can be used to create liposomes, including agitation, sonication, extrusion, lyophilization, freeze-thaw processing, reverse phase evaporation, the detergent depletion method, ether/ethanol injection, emulsification techniques, and a transmembrane pH gradient-driven encapsulation method. Modifications to these formulation parameters may have an impact on the ability of the liposomes to encapsulate drugs, as well as their permeability, stability, size, and lamellarity.

The mucoadhesive, nanocarrier intended for being the advantage of this sort of treatment in cervical cancer studies has been used in hybrid systems to address these

inadequacies. Studies have demonstrated that the liposome-chitosan nanocarrier system significantly increased the permeability of curcumin, producing a superior formulation in comparison to conventional systems of vaginal administration phospholipid-chitosan hybrid nanoliposomes promoting cell entry for drug delivery against cervical cancer.

Positively charged multi-layered liposomes with paclitaxel (PTX) loading were layer by layer built to help administer the lyophilized liposomal-chitosan formulation that followed (PAA-PTX). The in vitro release experiments showed that the liposomal chitosan formulation displayed regulated release of medication, and this formulation demonstrated higher cytotoxicity of PTX in human cancer cells when compared to PTX-liposomes. This system was stable in simulated gastrointestinal fluids.

Solid lipid nanoparticles

In the early 1990s, solid lipid nanoparticles (SLNs) emerged as a class of colloidal drug transporters with a wide range of clinical applications for drug delivery. Because they are aqueous colloidal dispersions with solid lipid matrixes that create biodegradable lipids, SLNs are the first generation of solid lipid matrix systems on the nanometric scale that are well tolerated by in vivo systems. These solid lipids include cetyl palmitate, beeswax PEG-8, cetyl palmitate, alba wax, carnauba wax, saturated glycerol esters, palmitic palmitate, and glyceryl Di behenate**.** These nanocarriers have the ability to modulate drug release, increase drug solubility, reduce dosage, improve stability by shielding chemically unstable chemicals, and provide binding and internalisation in tumour cells. This active targeting can also enhance SLNs distribution within the tumour vasculature and MDR cells.

Combination therapy

Drug resistance may develop in chemotherapy patients who consistently use a single medication. Within a few cycles, combination therapy using several different treatment modalities can lead to superior treatment outcomes. Even while using numerous chemotherapeutic treatments leads in less adverse side effects because of the modest dosage of each agent, combination therapy still has an additive effect. Recently, paclitaxel, bevacizumab, carboplatin, topotecan, and gemcitabine have been used as combination therapy for the treatment of cervical cancer. Treatment with cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab was more effective in patients with persistent, metastatic, and recurring cervical cancer. The effectiveness of treatment may be improved by using molecules or medications that target pathways involved in tumorigenicity as well as resistance pathways.

Gold Nanoparticles for Cervical Cancer Screening

For early precancer/cancer detection and early treatment, effective cervical cancer screening is crucial. Yet, in low-resource areas, cervical cancer screening initiatives have had only sporadic success. For the quick detection of the p16INK4a biomarker, we conceived and created a paper-based immunosensor with visual readout in 30 minutes for cervical cancer screening. The platform was created using the ASSURED philosophy, with a focus on accessibility and affordability in poor nations. The great sensitivity of our device was made possible by the employment of a novel multifunctionalized nanoparticle in our work, which was made of AuNPs attached with a particular antibody to the p16INK4a biomarker and conjugated with HRP enzyme. To further boost test sensitivity, we employed AuNPs-based peroxidase-like activity.

When AuNPs were combined with anti-p16INK4a-HRP as opposed to anti-p16INK4a-HRP alone, a positive signal was strengthened more. A highly sensitive cancer diagnostic test has recently been created using multifunctionalized gold or iron oxide nanoparticles. An ELISA-like test based on gold-enhance peroxidase-like immunogold activity was previously employed, and the results led to a 5-fold decrease in the LOD to detect human IgG. Comparable to a recently published lateral flow immunochromatographic (IC) test for identifying a distinct biomarker (E6/16-18 HPV), our immunosensor was created as an easy and economical screening tool. With a LOD of 3,000 cells, our p16INK4a test demonstrated greater sensitivity compared to the E6/16-18 IC test, which had a LOD of 150,000 cells for the SiHa cervical cancer e needed for our immunosensor test was lower (25 µl), while the sample amount needed for the lateral flow test was 200 l. Our p16INK4a test produced the greatest recorded accuracy of 85.2%, compared to 57.2% by ELISA for detecting CIN 3 precancer tissues and 72.8% in an immunohistochemistry study.

Dendrosome based delivery of siRNA against E6 and E7 oncogenes

Because to its clearly defined structure, small size (nanometric), and simplicity of surface modification, dendrimers have recently become innovative cationic nanocarriers for exogenous gene transfer into mammalian cells. PAMAM dendrimers, however, have had very sporadic effectiveness in siRNA delivery. Moreover, dendrimers' high level of toxicity is a significant barrier that has restricted their use in vivo. Dendrosomes have also been investigated for the transport of plasmid DNA since they are said to have greater transfection efficiency and little cytotoxicity. Consequently, it was thought that a dendrosomal formulation of siRNA would be stable and useful for the treatment of cervical cancer by silencing E6 and E7 oncogenes.

To maximise the production of dendrimer and N/P ratios, cellular uptake tests employing dendrimer-FITC oligo complexes were conducted. According to results of earlier research, it was found that the cellular absorption

of these complexes rises with dendrimer production and N/P ratio. It is evident that greater cellular absorption is strongly correlated with the quantity of terminal amino groups and the complex's overall positive charge. The N/P ratios from each generation of dendrimer that showed a high level of cellular absorption were chosen, and their capacity to knock down GFP was examined. It is clear from the study that dendrosomes are safe and effective delivery methods for siRNA in cervical cancer. These dendrosomes may become even more effective if appropriately targeted to particular cancer cells, making them attractive vectors for in vivo usage against cervical cancer and other genetic illnesses that call for tailored gene delivery.

Cisplatin loaded nanofibers for cervical cancer

Preparation of cisplatin loaded nanofibers; The optimal procedure for preparing an 18% w/v solution of polycaprolactone in DCM and DMF (6:4) involved dissolving 1.8 grammes of polycaprolactone in 10ml of DCM (6ml) and DMF (2ml) while stirring continuously for two hours. Separately, a saturated solution of cisplatin in 2ml DMF was made. Afterwards, cisplatin saturated solution was added to the polymeric solution. To achieve a homogeneous dispersion of medication in the created polymer combination, previously prepared 0.5 ml of the 1% w/v chitosan polymeric solution in 7% v/v trifluoroacetic acid was added drop by drop to the aforementioned solution. A 25-gauge needle with a 5-mL syringe attached was used to inject the polymer solution (inner diameter 0.25 mm) was subsequently set up in the electrospinning device. At room temperature, a longer pump was employed to deliver the polymer solution at a rate of 600 l/hr. At a voltage of 17 kV and a needle to collector gap distance of 15 cm, electrospinning was performed. The nanofibers were gathered on a thick layer of aluminium foil that was placed over the collector. The absence of beads or drips in the sheets and the modest, consistent diameter of the fibres were seen as successes.

Due to its many different uses, nanofiber has a huge possibility and potential to enhance localised drug delivery. The primary determinants of the drug release profile of the proposed formulation are poor water solubility and restricted erosion of Polycaprolactone under vaginal environment. In order to achieve a better site bioavailability of the medication in nanofiber than the plain drug solution, the mucoadhesive property of nanofiber is crucial. The fact that cisplatin was administered in its active condition was confirmed by in vivo activity, which also demonstrated significant effects against cervical cancer caused by EAC cells in Swiss albino mice. Moreover, advances in polymer science and a straightforward electrospinning technology allow for the fabrication and modification of nanofiber characteristics to obtain desired medicinal and pharmacological qualities of encapsulated materials.

Nanotubes in cervical cancer treatment the structural family of fullerenes includes nanotubes. They are known as graphene because of their hollow, extended structure with walls made of carbon that are just one atom thick. Specific and discrete ('chiral') angles, rolling angle, and radius all affect the characteristics of nanotubes. The number of walls in a nanotube determines its classification, such as single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs)

The anticancer drug doxorubicin (DOX), which was bound at pH 7.4 and released at a lower pH, lysosomal pH, and pH environment of some malignancies, was loaded onto single-walled carbon nanotubes (SWCNTs), derivatized with carboxylate groups, and coated with a polysaccharide substance by Zhang et al. In contrast to free DOX, folic acid, a targeting agent, was tethered to the SWCNTs to more effectively transport DOX to HeLa cells' lysosomes. The chemical (dox), which was released from the altered nanotubes, damaged nuclear DNA and slowed cell division.

Micelles in cervical cancer treatment

Amphiphilic block copolymers that can self-assemble into polymeric micelles are colloidal particles. Due to their in vivo stability, capacity to solubilize pharmaceuticals that are water-insoluble, ability to prolong the duration that blood circulates, and small size of 10-100 nm, they are essential for cancer therapeutic applications.

In order to increase the cytotoxic effect of two anticancer drugs (Palbociclib and Crizotinib), De Melo-Diogo et al. created "D-tocopheryl polyethylene glycol 1000 succinate-poly (lactic acid)" (TPGS-PLA)-based micelles containing sildenafil (an intracellular drug accumulation enhancer). In compared to single or double drug combinative micelles, triple drug-loaded TPGS-PLA micelles demonstrated improved cytotoxicity against A549 lung cancer cells and were described as innovative drug carriers for multiple drug therapy in the treatment of cancer.

Hydrogels as nanocarrier

Hydrogels are made of hydrophilic polymers distributed in water to create a polymeric mesh that conceals drug molecules inside. These polymeric meshes have a tendency to inflate to allow drug release for disintegration and dissolution outside of them. Gels used intravaginally contain medications and active substances that can restore physiological pH, moisturise and lubricate, function as a contraceptive or labour inducing agent, and/or have microbicide activity. They are well-established and well-known therapies. In addition to swellability, hydrogels include physical characteristics that can be changed by structural modifications, including mechanical resistance, permeability, surface characteristics, and biocompatibility.

A poly-(N-isopropylacrylamide)-chitosan-based nanohydrogel with Fe3O4 magnetic nanoparticles was created by Jaiswal et al. that is pH- and temperature-

sensitive (dual stimuli). The formulation was then tested for drug delivery and antineoplastic potential using doxorubicin as the model drug in in vitro drug release and cytotoxicity tests. Regarding the release of doxorubicin, the created system responded well to both triggers. Additionally, heating hydrogel-entrapped nanoparticles with an AC magnetic field while simultaneously exposing them to the cervical cancer (HeLa) cell line resulted to a notable decline in malignant cells.

Aptamer functionalised cisplatin-albumin nanoparticles; In this study, we engineered a special nanoparticulate system that improved the anticancer efficiency of loaded cisplatin medication by combining the intrinsic benefits of albumin nanoparticles and the targeting effects of RNA aptamers. There is a larger intracellular accumulation of cisplatin in tumour cells when NPs that are targeted by the aptamer are internalised via the receptor-mediated pathway than when non-targeted NPs are. The tumour was targeted in our system. The tumour locations could be readily reached by apt-Pt NPs. cisplatin might therefore be released intracellularly rather than extracellularly, preventing the needless build up in the body. and be further taken up by tumour cells. whereas free cisplatin was highly harmful to the spleen and kidneys. Aptamer-functionalized NPs would be a promising solution to the issue of cisplatin's systemic toxicity to normal cells, which consistently limits the therapeutic effectiveness of the drug in clinical studies. According to our study, Apt-Pt NPs greatly boosted rates of apoptosis and necrosis in vitro and in vivo when used as a treatment that combined gene therapy and chemotherapy, resulting in the highest tumour inhibition rates. The study also shown a significant reduction in associated toxicity to the kidney and spleen caused by the targeted administration of cisplatin by Apt-Pt NPs. As a type of medication delivery system, Apt-Pt NPs offer a number of benefits. The Apt-Pt NPs are initially biocompatible and degradable. Second, the NPs exhibit a significant capacity for drug loading and a stable regulated drug release. Thirdly, the NPs exhibit low toxicity while achieving high specificity, high affinity, superior tolerance, and higher efficacy.

Treatment options in recurrent cervical cancer; a challenging task for gynaecologic oncologists. While pelvic exenteration is typically the only therapeutic choice with a curative goal for women with central pelvic relapse following irradiation, patients with central or lateral pelvic failure after surgery alone can be treated with concurrent cisplatin-based chemoradiation. For isolated para-aortic lymph node recurrence, concurrent cisplatin-based chemo-radiation is the preferred treatment, with acceptable cure rates in asymptomatic patients. Patients who have localised or distant failures that are unresponsive to surgery or radiation therapy are given chemotherapy with the intention of providing palliative care. Comparing cisplatin-based combination chemotherapy to cisplatin as a single drug result in higher response rates, although median overall survival is typically less than a year. After salvage chemotherapy, certain cases of unexpectedly long-term disease-free survival have been documented in the literature. In a GOG (Gynecologic Oncology Group phase) III trial, individuals with metastatic, recurrent, or persistent cervical cancer who received topotecan with cisplatin had significantly longer progression-free survival and overall survival than those who received only cisplatin alone. In comparison to the triplets of cisplatin + topotecan, cisplatin + vinorelbine, and cisplatin + gemcitabine, the doublet of cisplatin + paclitaxel has been associated with longer overall survival and improved quality of life. Although its use alone or in conjunction with chemotherapy is still being studied, molecular-targeted treatment may represent a unique therapeutic strategy.

CONCLUSION

In conclusion, new treatment options for cervical cancer and HPV, which is a key contributor to incidences of this malignancy are desperately needed. Better outcomes in the treatment of cancer with conventional pharmacological therapy continue to be hampered by drug resistance. The more modern medication delivery technologies can overcome the resistance that conventional therapy provides. the nanocarriers mentioned in the study is important for the treatment of cervical cancer, and these nanocarriers have the following benefits: they increase drug solubility, reduce the number of doses needed, offer better stability, control and modulate drug release, have the ability to internalise and target to tumour cells with a volume-surface ratio that is susceptible to enzymatic activity and can be used in combination with other drugs. In a pre-clinical stage, more studies on animal models, particularly the cervical cancer model, should be conducted in addition to the toxicological studies, as nanocarriers-based formulations can be an appealing tool for the use, safety, and effective delivery of drugs.

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