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Review

Highlights in nanocarriers for the treatment against cervical cancer

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ABSTRACT

Cervical cancer is the second most common malignant tumor in women worldwide and has a high mortality rate, especially when it is associated with human papillomavirus (HPV). In US, an estimated 12,820 cases of invasive cervical cancer and an estimated 4210 deaths from this cancer will occur in 2017. With rare and very aggressive conventional treatments, one sees in the real need of new alternatives of therapy as the delivery of chemotherapeutic agents by nanocarriers using nanotechnology. This review covers different drug delivery systems applied in the treatment of cervical cancer, such as solid lipid nanoparticles (SNLs), liposomes, nanoemulsions and polymeric nanoparticles (PNPs). The main advantages of drug delivery thus improving pharmacological activity, improving solubility, bioavailability to bioavailability reducing toxicity in the target tissue by targeting of ligands, thus facilitating new innovative therapeutic technologies in a too much needed area. Among the main disadvantage is the still high cost of production of these nanocarriers. Therefore, the aim this paper is review the nanotechnology based drug delivery systems in the treatment of cervical cancer.

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1. Introduction

Cervical cancer is malignant carcinoma type of cancer originate in cervix region. The cervix is the narrow portion of the uterus where it joins with the top of the vagina. Most cervical cancers are squamous cell carcinomas, arising in the squamous epithelial cells that line the cervix. Approximately, 500,000 new cases of cervical cancer are diagnosed each year, with 280,000 deaths worldwide, making cervical cancer the second most common malignancy affecting women worldwide [1]. Clinical, epidemiological, and molecular data associate high-risk HPV infection with cervical cancer development [2].

Chemotherapy uses anti-cancer drugs that are injected into a vein or given by mouth by patients. These drugs enter the bloodstream and can reach all areas of the body, making this treatment useful for killing cancer cells in most parts of the body [3]. In recent years, drug delivery systems have been developed, along with anticancer agents for those systems based on the concept of achieving a better clinical response and tolerability [4,5]. From the aspect of pharmacokinetics, in particular drug distribution, these may cause low bioavailability of the anticancer drug at the site of action as well as high organ toxicity limiting the maximum tolerated dose [6].

Some important technological advantages of drug delivery systems include prolonged half-life, improved distribution, increased circulation time of the drug, controlled and sustained release of the drug, versatility of route of administration, increased intercellular concentration of drug [7] and a enhances the bioavailability of the poorly soluble drugs [8–10].

Liposome technology research culminated in 1995 in the U.S. Food and Drug Administration (FDA) approval of Doxil®, the first FDA-approved nanodrug [11]. After, other systems were approved as medicines and these commercialized drug delivery systems are listed in Table 1.

The effectiveness of a treatment can be increased by incorporating nanotechnology-based drug delivery systems. Some of these new platforms, which aim to improve the bioavailability, pharmacokinetics, and pharmacodynamics of drugs while reducing their side effects, or improving the selectivity in the tumor cells are discussed in this review.

2. Cervical cancer

Uterine cervical cancer is the second most common malignant tumor in women worldwide and presents a high mortality rate, especially in developing countries [19–21]. According to Kessler [22], cervical cancer has an incidence of 527,624 women/year, resulting in 265,672 deaths. In addition, cervical cancer accounts for 4% of the cases of cancer diagnosed in the world. About 84% of cervical cancer cases occur in less developed countries, such as Africa, Latin America and the Caribbean.

In Brazil it is the second most frequent in women population and the incidence and mortality, according to Brazilian Cancer Foundation [23], is, approximately, 530,000 new cases and 275,000 deaths each year in young women [24].

Cervical cancer is associated with high-risk human papillomavirus (HPV) and is responsible for causing benign lesions (genital warts or papilloma) or malignant lesions. HPV has been associated with more than 90% of cervical and anal cancers, 70% of the vaginal and vulvar cancers, caused by high-risk HPV, such as types 16 and 18 [25,26].

HPV is a public health problem that primarily affects undeveloping countries, where the population with low social status and poor hygiene habits becomes the main focus of viral infection that progresses to malignancy [19]. Infection with high-risk oncogenic subtypes of HPV is the major risk factor for the development of malignant lesions in the cervix. Although HPV infection may be the triggering factor, studies show that a linkage between genetic factors and immune functions are correlated to cervical carcinogenesis and infection by the major subtypes of high-risk [27].

Over 200 types of HPV have been isolated, and there is no doubt that there are other types that have not been identified. HPV leads to large epithelial lesions, mostly benign, such as warts or papillomas, with low malignant potential. A small fraction of people infected with the type of high-risk HPV will develop cancer, which usually arise many years after initial infection [28]. There are about 30 types of HPV and genital mucosa divided into low risk (types 6, 11, 42, 43 and 44) and high risk that are associated with precancerous lesions (types 16, 18, 31, 33, 35, 45, 51, 52 and 56), according to their presence in malignant lesions of the cervix [29].

Only a small number of women with chronic HPV infection can progress and develop disease [30]. In addition to HPV infection, other factors can trigger cervical cancer, such as malignant and invasive phenotypic factors, smoking and benzo[*a*]pyrene, BaP carcinogenic smoke [30,31].

HPV proteins, particularly E6 and E7, integrate DNA viral genes (antigens) into human DNA which are responsible for the development of malignant form and tumor growth, for this reason the development of vaccines against this type of proteins [32].

Three main methods are used in the treatment of tumors: surgical procedures, radiotherapy and chemotherapy, and these can be used with curative, palliative or prophylactic purposes, alone or combined [33–36].

The surgical procedure is very particularly between patients since it depends on the age, size, stage of disease and the patient's response to post-surgical. Radiotherapy combat the disease by ionizing radiation, which depends on the characteristics of cancer and patient being difficult to control damage to any adjacent normal tissue cell. Currently, it is common the use of combined chemotherapist to enhance the desired effect and to low the toxicity.

Recently, two prophylactic vaccines against HPV, Gardasil® and Cervarix® have demonstrated efficacy as preventive vaccines, 2 which act to produce antibodies against HPV serotypes types 6, 11, 16 and 18 (Gardasil®) and 16, 18 (Cervarix 16 and 18) [37–39].

However, these conventional treatments are very aggressive or nonspecific [234]. Currently, cancer research focuses on improving cervical cancer therapy by focusing on other treatment such as the delivery of chemotherapeutic agents by nanocarriers using the nanotechnology [40–42].

3. Nanotechnology-based drug delivery systems

Nanotechnology has offered many advances in the area of science especially in the area of pharmaceutical nanotechnology. Pharmaceutical and Materials sciences leads to the innovation of drug delivery thereby improving the pharmacological activity, reducing toxicity and

Table 1
Approved drugs commonly referred to as drug delivery systems.

Drug	Delivery system	Proprietary name	Indication	Approval (year)[a]	Reference
Doxorubicin	Liposome	Doxil®	AIDS-related Kaposi's sarcoma	1995	[12,13]
Daunorubicin	Liposome	Daunoxome®	AIDS-related Kaposi's sarcoma	1996	[14]
Amphotericin B	Liposome	Ambisome®	Antifungal agent	1997	[15]
Cytarabine	Liposome	Depocyt®	Lymphomatous meningitis	1999	[16]
Paclitaxel	Albumin-conjugated	Abraxane®	Metastatic breast cancer	2005	[17]
Vincristine	Liposome	Marqibo®	Acute lymphoblastic leukemia	2012	[18]

[a] Food and Drug Administration (FDA) in U.S.