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Breast Cancer and the Role of Polymer-Carriers in Treatment

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ABSTRACT

Every day we see progress in medicine and the treatment of many diseases. Cancer has been associated with human life for more than two decade and every day, many people in different parts of the world are going to die cause of cancer. Breast cancer is the most common among women. However, with the advancement of medical science, many cases can be treated. There are several sciences involved in this treatment, one of which is polymer engineering. Polymers have many applications in the treatment field for reasons such as biodistribution and biocompatible. Also, polymers are unique candidates for the release of anticancer drugs. This study briefly introduces breast cancer and several polymer-carriers.

Abbreviations: 1-MT: 1-Methyl Tryptophan; IDO: Indoleamine 2,3-Dioxygenase; DOX: Doxorubicin; PEG: Polyethylene Glycol; DTX: Docetaxel; IONP: Iron Oxide Nanoparticles; PK: Pharmacokinetic; NGs: Nanogels; Bcl-2: B-Cell Lymphoma 2; SiRNA: Small Interference RNA; MPN: Mesoporous Polymer Nanosphere; BC: Breast Cancer; EPI: Epirubicin; ALNM: Axillary Lymph Node Metastasis; TNBC: Triple Negative Breast Cancer

Mini Review

Cancer is one of the leading causes of death in the world and is the third leading cause of death in most countries after traffic accidents and cardiovascular mortality [1-4]. Cancer has become a major public health problem in the world and every day, many people in different parts of the world are going to die cause of cancer [5,6]. Also, cancer and its treatment can weaken the immune system and reduce the ability to fight infections, thus increasing the risk of death from infectious disease [7]. In recent years, with increased greenhouse gases and weather change, and environmental pollution, human health is increasingly at risk and the incidence of cancer has risen in some countries [8-20]. Breast, colorectal, and stomach cancers are the most common cancers for women, and stomach, prostate, and colorectal cancers are the most common cancers in men [21,22]. Breast cancer is known as the most common malignancy among women and causes many deaths every year [23]. Despite many advances in the early diagnosis and proper treatment of this disease, it is still the leading cause of death among women [24-26]. The disease originates from breast tissue cells. When normal cells in the breast begin to change and grow uncontrollably and they form tumors, at which point cancer begins [27]. The tumor is identified after the biopsy as non-cancerous or malignant. Breast cancer affects women between the ages of 15 and 85. Studies have shown that patients with breast cancer are exposed to a lot of stress that can cause psychological and social disorders in their lives.

The most important risk factors for breast cancer are age, sex, family history of cancer, and hormonal factors. Fortunately, cancer treatment has progressed amazingly, surgery, chemotherapy, and radiotherapy can destroy tumors and arrest cancer progression [28,29]. In recent years, the use of nanotechnology to diagnose and treat cancer has made significant progress [30-32]. Nanoparticles have the ability to penetrate cancer cells and can increase the concentration of drugs in them [33,34]. Carbon nanomaterials such as nanotubes, expanded graphite, graphene, and graphene oxide are

among the nanoparticles that due to their unique properties, have many applications in the field of nanocomposites and medicine [35-39]. Some of their medical applications include colorimetric detection of cancer cells, and cancer imaging [40,41]. Also, polymers have many applications in the medical field for reasons such as biodistribution and biocompatible [42-48]. They can be good carriers and prevent premature destruction of the drug and improve their stability and prolong the presence of the drug in the circulatory system [49-53]. In addition, polymers can carry multiple drugs at the same time, which can be very useful for treatment [54-57]. Polymeric carriers have the ability to release drugs with changes such as temperature, pH, etc [58-61]. In recent years, a lot of research has been done on this field. Lan, et al. [62] they studied the novel dual-functional immunostimulatory polymeric prodrug carrier PEG2k-Fmoc-1-MT was developed for simultaneously delivering 1-Methyl Tryptophan (1-MT) of an Indoleamine 2,3-Dioxygenase (IDO) inhibitor and chemotherapeutic Doxorubicin (DOX) for breast cancer immunochemotherapy. Micelles were more effective in cell proliferation inhibition and apoptosis induction in 4T1 cells. PEG2K-Fmoc-1-MT prodrug carrier has an average particle size of 298.5 nm. Loading of DOX into PEG2K-Fmoc-1-MT prodrug carrier showed a decrease average particle size, ranging from 281.0 to 148.6 nm with carrier/drug molar ratios of 1/1 to 5/1, respectively.

Micelles exhibited prolonged blood circulation time and superior accumulation of DOX and 1-MT in tumors compared to that of DOX and 1-MT solutions. Micelles exhibited prolonged blood circulation time and superior accumulation of DOX and 1-MT in tumors compared to that of DOX and 1-MT solutions. Also, the coreleased DOX-triggered immunogenic cell death action combined with the cleaved 1-MT promoted the related cytokine secretion of tumor necrosis factor-α, interleukin-2, and interferon-γ, further facilitating the T cell-mediated immune responses. Moreover, the DOX-loaded micelles led to a significantly improved inhibition on tumor growth and prolonged animal survival rate in a 4T1 murine breast cancer model. Panda, et al. [63] they studied the biocompatible nano-drug delivery formulation based on poly (D, L-lactide-co-glycolic) acid (PLGA), Polyethylene Glycol (PEG), and superparamagnetic iron oxide nanoparticles have been developed and evaluated for the enhanced delivery of Docetaxel (DTX) to breast cancer cells. For this purpose, the hydrothermally synthesized Iron Oxide Nanoparticles (IONP) were encapsulated along with the DTX drug in a PLGA-PEG coating using a modified emulsion evaporation method. The DTX loaded Iron Oxide Nanoparticles (DIONP) showed spherical shape and uniform size distribution in the range of 160-220 nm. Also, in vivo plasma Pharmacokinetic (PK) study showed improved values of important PK parameters such as area under curve, mean residence time, the volume of distribution, etc. for DIONP as compared to pure DTX. DIONP showed nearly 12% drug loading capacity with a sustained drug release over the experimental time period. Cuggino, et al. [64] they studied the N-isopropyacrylamide/acrylic acid Nanogels (NGs), NIPA/AAc NGs, crosslinked by a disulfide-bearing monomer, which can be used as smart carriers of DOX. NGs showed a spherical morphology of approximately 50 nm diameter in dry state with a relative narrow distribution. The mean size of the NGs was 79.3 nm (PDI 0.076) at simulated plasma conditions and 59.3 nm (PDI 0.065) at simulated intracellular conditions, respectively.

This designed drug delivery system can active the release of a large amount of drug in simulated intracellular medium in response to redox potential and pH, but with minimal release in simulated plasma conditions. Also, NGs loaded with DOX can be internalized in human breast cancer cell line MDA-MB-231. Unloaded NGs are nontoxic for human breast cancer cell line MDA-MB-231 and mouse breast cancer cell line 4T1. In addition, it was shown that DOX-loaded NGs are more toxic for the cell than free DOX for both cell lines. In vivo studies in mice showed that DOX-loaded NGs improve the drug therapeutic index with a notable decrease in tumor size, as compared with a similar dose of free DOX. Wu, et al. [65] they studied the nanomedicine system is constructed using B-cell lymphoma 2 (Bcl-2) Small Interference RNA (siRNA) as the therapeutic agent and Mesoporous Polymer Nanosphere (MPN) carriers to both improve cellular internalization and achieve Bcl-2 silencing and cell apoptosis. MPNs were prepared through a two-stage hydrothermal process at two different temperatures. MPNs have a spherical morphology, ordered mesoporous structure, good dispersion, and narrow size distribution in the range of 50 to 120 nm, and that the mesopores possessed a parallel channel structure with an average mesopore diameter of approximately 6 nm. FA-targeted-Bcl-2-siRNA-loaded nanoparticles were constructed by a layer-by-layer assembly by electrostatic interactions after nitrification. These nanoparticles were efficiently delivered into Breast Cancer (BC) cells, showing significant sequence-specific inhibition of Bcl-2 mRNA expression in BC cells, enhanced tumor cell apoptosis and tumor therapeutic efficacy. Nicolas, et al. [66] they studied the impact of calcitriol encapsulation on its antiproliferative activity and optimized formulation parameters with that respect. Calcitriol-loaded polymeric nanoparticles with different polymer: oil ratios were prepared by the nanoprecipitation method. nanoparticles showed uniform size distribution in the range of 220 nm whereas their release profile strongly depended on formulation parameters.

Antiproliferative and cytotoxic activities of formulated calcitriol were evaluated in vitro using human breast adenocarcinoma cells (MCF-7) and showed that calcitriol-induced cell growth inhibition was closely related to its release kinetics. For the most suitable formulation, a sustained cell growth inhibition was observed over 10 days compared to free form. Chida, et al. [67] they studied the therapeutic effect of an anthracycline drug, Epirubicin (EPI)-loaded polymeric micelles equipped with pH-triggered drug release property (EPI/m) against Axillary Lymph Node Metastasis (ALNM)

of Triple Negative Breast Cancer (TNBC). EPI/m effectively inhibited the spread of the primary tumor and the growth of ALNM, through selective accumulation and penetration in both primary tumor and vascularized ALNM, as well as efficient drug activation triggered by the intratumoral acidic environment. Also, the improvement of the activated drug distribution of EPI/m contributed to dose-dependent enhancement of the antitumor effect through expansion of the therapeutic window. Finally, polymers are good candidates for the diagnosis and treatment of cancer, they are commonly used to release drugs such as doxorubicin, paclitaxel, methotrexate, nystatin, vinblastine, cisplatin, rapamycin, fenofibrate, and carvedilol [68-70].

Conclusion

Polymers can create a good future for cancer treatment. Polymeric carriers have the ability to load multiple drugs simultaneously and can increase drug concentrations by penetrating the target tissue. They can be used to reduce the steps of chemotherapy. Many cancer drugs have many side effects that can cause a lot of damage to healthy cells, but with the use of polymer-carriers, the side effects of the drug are minimized, this is due to the delivery of the drug is delivered to the target tissue, which prevents the drug from affecting other cells.

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