Nanodrugs For Cancer Therapy

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Abstract
Nano sized and targeted drugs have emerged as promising materials for the treatment of cancer. Traditionally used chemotherapy drugs have some disadvantages such as low drug loading capacity, uncontrolled structure, high reticuloendothelial system (RES) accumulation, unpredictable metabolic mechanism. In order to overcome these problems, nanoparticle based anticancer drugs have received great attention recently. Unlike traditionally used anticancer drugs, nanoparticle based anticancer drugs provide unique advantages such as simple synthesis, specific structure, high drug loading capacity, excellent accumulation in the tumor and low toxic effect. Therefore, drugs with high side effects and high therapeutic efficacy in cancer can be administered in the future with nanoparticles. Until now, significant progress has been made in the investigation of nanodrugs for use in the treatment of cancer. The biological properties and application of nanoparticle based drugs for cancer treatment summarized briefly in this review.

1. Introduction
1.1. Cancer

Cancer is the proliferation of cells in an uncontrolled or abnormal manner due to damage of DNA in normal cells (1). Cancer also appears as a result of the failure of mechanisms to control normal division in a group of cells (2). Nowadays, the majority of deaths are caused by cancers. Environmental ant genetic factors increase high risk of cancer development (3). According to data from the international cancer research center, in 2008, 7.6 million people died of cancer among 12.7 million cancer patients in the world, whereas in 2012, 8.2 million people died from 14.1 million cancer patients. In 2025, cancer-related deaths are estimated to be 19.3 million (4). Breast cancer in women, prostate cancer in men is the most common and diagnosed with the leading cause of death cancers (Fig.1). Colorectal cancer is the third most common and fatal cancer in males and the second in females (5, 6). For this reason, scientists are making great efforts to treat cancer, but there has been little progress in cancer therapy over the past 50 years. To significantly improve effective cancer treatment methods, we must greatly

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improve our knowledge of cancer pathophysiology, discover new anticancer drugs and develop new biomedical technologies. As a result, cancer treatment has become a multidisciplinary problem that requires close cooperation between clinicians, biology and chemical scientists, biomedical engineers (7).

Figure 1. Leading types of cancer in predicted new cancer cases in males and females

1.2. Cancer and Therapy
In cancer treatment, surgery, radiotherapy and chemotherapy are the main treatment methods. There has been enormous progress over the past few decades in cancer therapy. Chemotherapy treatment among various therapeutics based on high cytotoxicity of chemotherapeutic agents against cancer cells has become a dominant for most cancer methods due to its high efficiency compared to other treatments (8). But, traditionally used chemotherapeutic agents and drugs affect the whole body system by blood, and there are many systematic side effects such as tissue damage, gastrointestinal stress. But, the body begins to develop resistance to chemotherapeutic agents. Because chemotherapy drugs did not reach the targeted tumor sites and cancer cells were very similar to normal cells, scientists needed to develop new drugs (9). Despite the modern treatment protocols, combined chemotherapy, surgery and sometimes chemotherapy, the five-year survival rate is between 60% and 70%. (10). Therefore, it is important to better understand the underlying tumor progression and metastasis mechanisms to identify or develop more effective therapies. In cancer cell lines and tissue samples, these mechanisms are important tools for studying and evaluating new targeted therapies (11). However, one of the main problems is the emergence of systemic toxicity due to the inability of drugs to distinguish between cancerous and normal cells (12). For such reasons, new antitumor chemotherapy was provided by the development of nanostructures for the development and controlled release of drugs (13).

1.3. Cancer and Drug Resistance
Drug resistance is a phenomenon known to occur when diseases are tolerant to pharmaceutical treatments. Some drug resistance developments are disease-specific (14). The anticancer drugs efficiency and their activity are dependent on the complex mechanisms. The interaction between drugs and different proteins can alter the molecular properties of drugs and ultimately activate them. Cancer cells become resistant by reducing the activity of drugs (15). Although many types
of cancer initially respond to chemotherapy, they may develop resistance through many mechanisms, such as metabolic changes that promote DNA inhibitions, drug inhibition, and degradation (Fig. 2) (14).

**Figure 2.** Mechanism categories that directly or indirectly support drug resistance in human cancer cells. These mechanisms act independently or in combination and act through various signal transduction pathways to contribute to drug resistance (14).

The development of resistance to chemotherapeutic drugs may occur at the time of diagnosis or may develop after treatment with chemotherapy. This drug can be of two kinds of development of resistance, they are called intrinsic and acquired respectively. It is unknown whether the mechanisms underlying drug resistance are linked to these two forms of drug resistance. The development of resistance-enhanced cancer cell lines by exposure to increasing concentrations of anticancer drugs has made it possible to identify a number of mechanisms underlying cellular drug resistance (16). Some of these mechanisms, such as loss of cell surface receptor or carrier for a drug, specific metabolism of a drug, or a mutation of a specific target of a drug, occur, for example, for antifolates such as methotrexate and result in resistance (17). In this case, drug resistance can be caused by mutations that reduce the expression of surface receptors or carriers, nucleoside transporters, or one or both folate transporters that modify the activity (17, 18-22).

Resistance to chemotherapy is the leading cause of multidrug resistance (MDR) in particular. The mechanism of MDR is highly complex, including increased drug flow, drug metabolic biotransformation, and the ability to repair for DNA damage caused by anticancer drugs (23). Mutations of apoptosis-dependent genes and cytokinetic factors also induce the development of resistance to antitumor drugs (24). It is important to understand that multiple different mechanisms are likely to contribute to clinical MDR. The expression of P glycoprotein (P-gp) in the membrane of cancer cells is considered the main mechanism of MDR (25). P-gp is a 170 kDa plasma membrane protein and is encoded by the multidrug resistance gene 1 (MDR-1). The P-gp protein promotes excretion of chemotherapeutic drugs in tumor cells and thus serves as an energy-dependent outlet pump, which reduces drug cytotoxicity (26-28). P-gp is a transmembrane protein found in tumors and normal cells. Anticancer drugs are responsible for the active transport of many physiological substances, such as cells from the cell cytosol. By active drug
extrusion, the drug concentration at the intracellular target site is insufficient, thereby resistance occurs (29,30).

1.4. Cancer and Nanotechnology

With nanotechnology, it is aimed to reduce the existing technologies and to create more sensitive systems. It is possible to use nano-sized products in many fields such as medicine, chemistry and biotechnology. The production of various nanoparticles for the development of anti-cancer drugs has been one of the most important areas of nanomedicine. The emergence of nanomaterials and the vast majority of studies are the result of interdisciplinary studies. While the nanomaterials are synthesized in various properties, especially in medicine and biotechnological fields, it is noteworthy that the joint work of different disciplines is remarkable. The structures described as nanosize are divided into different classes such as nanocrystals, nanoparticles, nanotubes, nanowires, nanorods. It is basically called nanoparticle. NPs are tiny materials having size ranges from 1 to 100 nm. They can be classified into different classes based on their properties, shapes or sizes (31,32). Nanoparticles have unique physical and chemical properties due to their high surface area, their surface area / volume ratio and nanoscale size and possess a functional group. Since nanoparticles have very small diameters, they have been preferred in both in vitro and in vivo studies in the field of health, biomedical and pharmaceutical applications particularly cancer diagnosis and treatment, targeted drug release, biosensors, etc. in recent years. Especially in the diagnosis and treatment of cancer, the high side effects of the drugs used in chemotherapy, not to reach the targeted areas and cancer cells as well as the destruction of healthy cells due to the disadvantages of studies in these areas has gained importance.

The nanomaterials that are present in cancer research can be changed in size, shape and surface properties for use in the treatment of specific tumors. The size of the nanomaterials is important to transport through the bloodstream and to ensure that the nanocarriers based drugs are present in the tumor tissue and to increase the amount. Smaller nanoparticles may accumulate more easily in leaking blood vessels of tumors than larger particles, whereas they may be extravasated to normal tissue. On the other hand, larger nanoparticles cannot extravasate as easily and thus their distribution in the bloodstream is highly variable. The optimization of the nanoparticle size can help the drug to be specifically involved in tumor tissue. The shape of the nanocarriers may impact fluid dynamics and thus influence uptake. Chemotherapy is an important therapeutic approach for the treatment of a wide variety of cancers (33-36) However, undesirable effects of chemotherapeutic agents on all body cells cause undesirable side effects in normal tissues and cause insufficient dosages to kill cancer cells. For this reason, targeted drug release to overcome these challenges has been reported by Abou-Jawde et al (37-39) and combined therapies (40-42) was developed.

The use of nanomedicines are being researched in anticancer therapies to improve the efficacy of treatment, reduce side effects and overcome drug resistance. Figure 3 shows the number of studies published under the research topics of “nanodrug” and “cancer” in the last decade. The number of studies is gradually increasing with a slight decrease in 2018. As more nanodrugs were discovered and their potentials
were better understood, the number of publications increased and reached its peak in 2017. Presently, the knowledge base of nanodrugs is still expanding with an emphasis on safety and efficacy.

**Figure 3.** The number of references under the research topics of "nanodrug" and "cancer" from 2005 to 2018. The number of publications peaked in 2017 with 81 and saw a slight decline in 2018 with 74 publications.

Clinical application of nano-drugs with combination therapies can provide a very useful opportunity for early detection of cancers and earlier and more effective treatment of tumors. Presently, a wide variety of platforms for the treatment of cancer, including lipid-based, polymer-based, inorganic, viral and drug-conjugated nanoparticles for combination therapy, are being investigated (Fig. 4).

**Figure 4.** Overview of established nanomedicines in the clinic. This diagram shows an overview of the nanomedicines currently being investigated in the clinic for cancer treatment.
Over the past several decades, studies have been accelerated in the use of nanoparticles for effective drug delivery in cancer treatment studies. Various nanoparticles and polymer based nanodrugs have been used in drug delivery research as they can effectively deliver the drugs to the target site thus increases the therapeutic benefit, while minimizing side effects. The controlled release of pharmacologically active drugs to the precise action site at the therapeutically optimum degree and dose regimen has been a major goal in designing nanodrugs.

2. Conclusion

In this review, we summarized some novel nanotechnology based drug delivery systems applications in the field of cancer therapy. Nanomedicine is a new field to help effective cancer treatment worldwide. In the treatment of cancer with nanomedicines, it is thought that many advantages such as increased circulation time of the drug, sensitive multi-targeting mechanisms, increased drug accumulation in the tumor area, and the ability to overcome MDR. Numerous unique nano-drugs have been extensively studied in the literature and are in clinical development. When studies and optimizations on nano-drugs continue particularly in vivo, the available treatment options in drug-resistant cancers and the superiority over conventional drugs will continue to rise and these drugs will be a hope. In the future, traditionally used cancer drugs and nanoparticle-based drugs can be studied for cancer diagnosis and treatment both in vitro and in vivo.

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