A COMPREHENSIVE REVIEW ON THERAPEUTIC APPROACHES OF NANO PARTICLES IN CANCER THERAPY

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ABSTRACT:

Nanotechnology has been extensively studied and exploited for cancer treatment as nanoparticles can play a significant role as a drug delivery system. Compared to conventional drugs, nanoparticle-based drug delivery has specific advantages, such as improved stability and biocompatibility, enhanced permeability and retention effect, and precise targeting. The application and development of hybrid nanoparticles, which incorporates the combined properties of different nanoparticles, has led this type of drug-carrier system to the next level. In addition, nanoparticle-based drug delivery systems have been shown to play a role in overcoming cancer-related drug resistance. The mechanisms of cancer drug resistance include overexpression of drug efflux transporters, defective apoptotic pathways, and hypoxic environment. Nanoparticles targeting these mechanisms can lead to an improvement in the reversal of multidrug resistance. Furthermore, as more tumor drug resistance mechanisms are revealed, nanoparticles are increasingly being developed to target these mechanisms. Moreover, scientists have recently started to investigate the role of nanoparticles in immunotherapy, which plays a more important role in cancer treatment. In this review, we discuss the roles of nanoparticles and hybrid nanoparticles for drug delivery in chemotherapy, targeted therapy, and immunotherapy and describe the targeting mechanism of nanoparticle-based drug delivery as well as its function on reversing drug resistance.

Cancer is a disease with complex pathological process. Current chemotherapy faces problems such as lack of specificity, cytotoxicity, induction of multi-drug resistance and stem like cells growth. Nanomaterials are materials in the nanorange 1–100 nm which possess unique optical, magnetic, and electrical properties. Nanomaterials used in cancer therapy can be classified into several main categories. Targeting cancer cells, tumor microenvironment, and immune system, these nanomaterials have been modified for a wide range of cancer therapies to overcome toxicity and lack of specificity, enhance drug capacity as well as bioavailability.

Keywords: Nanoparticle, drug delivery, hybrid nanoparticles, targeted cancer therapy, drug resistance.

INTRODUCTION:

Cancer is the second most common cause of death around the globe. It killed 9.6 million people in 2018. According to the WHO, one in five men and one in six women will develop cancer in their life and one in eight men and one in 11 women will die from this serious disease. Several methods have been developed for treatment, but there are still no available approaches that can completely eradicate this life-threatening disease. Cancer therapy is currently mostly limited to surgery, radiation, and chemotherapy, but they each have several disadvantages and often fail to cure the condition. Recently, nanomaterials have attracted much attention from scientists interested in cancer therapy because of their versatile physical and chemical properties. Many reports have focused on the use of nanomaterials as carriers of therapeutic compounds. These therapeutic systems have been extended by introducing external stimuli (e.g., light, magnetic waves, and heat) to improve drug release at the tumor sites. These approaches can be further subdivided into photodynamic, photothermal, magnetic, and neutron-capturing systems. Unfortunately, the use of nanomaterials as carriers of therapeutic compounds has some flaws, which preclude these therapeutic systems from clinical applications. The major challenges are a low drug loading efficiency, low solubility in an aqueous media, poor ability to cross in vivo barriers and penetrate inside the tumor (less than 1% reach the tumor), problematic physical and chemical interactions of hydrophobic therapeutic compounds with nanomaterials, in vivo instability, a suboptimal biodistribution, low tumor targeting ability, and a suboptimal drug release profile. To minimize all of these issues and bring nanomaterials from the bench to clinics, scientists are trying to develop optimized self-therapeutic nanomaterials that can work like a “magic nano bullet” without the loading of additional therapeutic compounds or external stimuli dependency to make these systems practical for clinical applications. Most of the organic nanoparticles (liposomes, micelles, exosomes, lipids, PLA, PLGA),inorganic nanoparticles (gold, silver, silica, iron, graphene, carbon quantum dots), and composites (metal−organic frameworks (MOF), transition metals dichalcogenide (TMD)) were designed as carriers in drug-delivery systems or for use in external stimuli-based systems such as photodynamic therapy (PDT),photothermal therapy (PTT),magnetic therapy, and boron neutron capturing therapy (BNCP).All these external dependencies and low loading efficiency of therapeutic compounds are
Shortcomings, which has led to the failure of these systems at

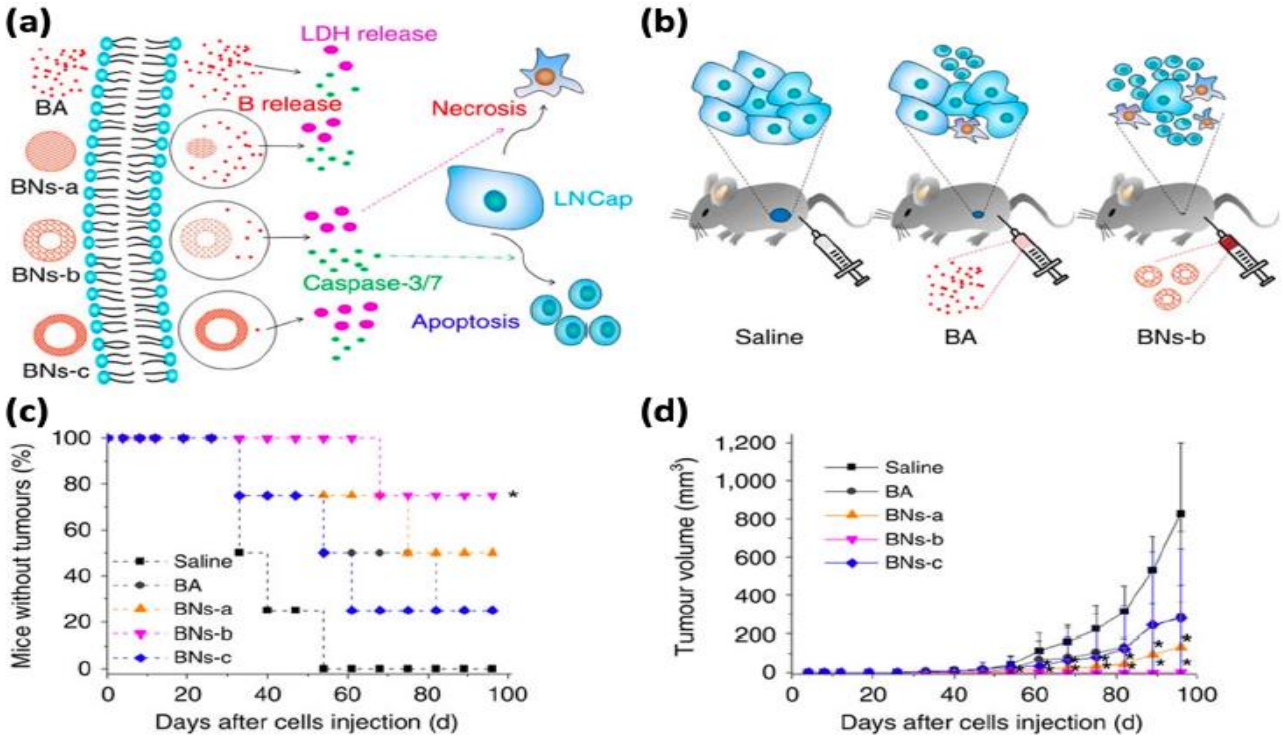

Figure 1. In vitro and in vivo effects of boron nitride nanospheres (BNs). (a) Different levels of necrosis (LDH) and apoptosis (caspase 3/7) in prostate cancer cells due to the release of boron from BA or hollow BN spheres. (b) BNS, BA, and saline effects on LNCap mouse tumor models. (c) Effect of different formulations of boron on the inhibition of tumor growth and (d) tumor volume in mice models. Reproduced with permission from ref 23. Copyright 2017 Springer Nature.

The clinical level. Additionally, these therapeutic systems need specific special equipment that is difficult to use and requires confining the patient in the hospital. In this review, we will go over the available data on nanotherapeutic systems derived directly from nanomaterials through some specific mechanisms (using the intrinsic properties of the materials) and discuss the possible future uses of these systems.

History of Cancer:

Cancer is a main leading cause of death all over the world, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. The most common cancers are breast, lung, colon and rectum and prostate cancers. Around one-third of deaths from cancer are due to tobacco use, high body mass index, alcohol consumption, low fruit and vegetable intake, and lack of physical activity. Cancer-causing infections, such as human papillomavirus (HPV) and hepatitis, cause approximately 30% of cancer cases in low- and lower-middle-income countries.

WHO Statistics:

Cancer is a main leading cause of death all over the world, accounting for nearly 10 million deaths in 2020. The most common cancers in 2020 (in terms of new cases of cancer) were breast (2.26 million cases); lung (2.21 million cases); colon and rectum (1.93 million cases); prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases); and stomach (1.09 million cases). The most common causes of cancer death in 2020 were: lung (1.80 million deaths); colon and rectum (916 000 deaths); liver (830 000 deaths); stomach (769 000 deaths); and breast (685 000 deaths). Every year, we notice approximately 400 000 children develop cancer. The most common cancers vary between countries. The most common cancer all over the 23 countries was Cervical cancer.

Treatment Options for Cancer:

There are many types of cancer treatment. The types of treatment that you receive will depend on the type of cancer you have and how advanced it is and here are the treatments listed for cancer : Biomarker Testing, Chemotherapy, Hormone Therapy, Hyperthermia, Immunotherapy, Photodynamic Therapy, Radiation Therapy, Stem Cell Transplant, Surgery, Targeted Therapy.

Advantages:
By taking the Cancer Therapy it may shrink your cancer or slow down the growth of the cancer affecting cells, which may help you live longer and help with your symptoms. For a small number of people with borderline resectable cancer, chemotherapy may shrink the cancer enough to make surgery to remove the cancer possible. The chances of getting back from the cancer may reduce in case

you have taken the chemotherapy after surgery. You may have more regular check-ups, tests and contact with your doctor when you are having chemotherapy. Some people find this reassuring.

Disadvantages:
Chemotherapy can cause side effects. You will need to go to the hospital often for treatment, check-ups and tests, possibly on different days, which can be tiring. Chemotherapy affects everyone differently and may not work so well for some people.

Statistics of cancer & Treatment options of cancer:

Cancer is a very complex disease that develops through a multistep process which includes resistance to cell death (apoptosis), uncontrolled cell growth, alterations in cellular signaling, tissue invasion, metastasis, and angiogenesis.1 Cancer generally begins as a localized tumor and can spread (metastasize) to distant sites in the body, making the management difficult. Cancer morbidity and mortality are on the rise across the world. According to global cancer incidence, mortality, and prevalence (GLOBOCAN) 2018 data, the number of new cancer cases was expected to exceed 18.1 million, with 9.6 million cancer-related deaths.2 The World Health Organization (WHO) estimated more than 19.3 million new cases and 10 million deaths from cancer in 2020.

It is projected that 30 million people will die of cancer each year after 2030.Factors that enhance the emergence of cancer include rising pollution, radiation, sedentary life, unbalanced diet, infection with oncogenic microorganisms, and other variables (e.g., heredity) which are also becoming common in developing countries. Any of these variables can cause damage in host cells' deoxyribose nucleic acid (DNA) genes known as oncogenes that lead to cancer. Individual cells that have achieved immortality and are capable of replicating at incredible rates surpass all healthy functional cells resulting in death. Nanotechnology is the field that deals with atomic, molecular, and supramolecular levels of molecules (1–100 nm) to understand the properties that can be exploited for human well-being.

Nanotechnology uses nanoscale principles and methods to know biosystems, and it is being emerged with modern biology and medicine to generate more nanoscale materials that can be used in biological systems. Nanoparticles are used in medical applications because of their unique properties such as quantum properties, a surface-to-mass ratio much larger than that of other particles, and an adsorption capacity to transport other compounds such as probes, proteins, and drugs. The composition of nanoparticles can be varied, just as starting materials can be biological lipids, dextran, lactic acid, phospholipids, chitosan, or chemicals such as silica, carbon, metals, and different polymers.

Imaging techniques and morphological study of tissues (histopathology) or cells (cytology) are currently used to aid in the early detection of cancer. Imaging technologies enable to see tissue alterations for the detection of cancer cells. However, due to the time demanding nature of these methods, cancer cells can have time to replicate and invade tissue. Furthermore, existing imaging technologies are unable to discriminate between benign and malignant tumors. Besides, cytology and histopathology cannot be used to diagnose cancer at an early stage in a reliable and independent manner. As a result, developing reliable methods that can detect cancer at an early stage is necessary.

Nanotechnology-based diagnostic technologies are being developed as promising tools for cancer diagnosis that are real-time, convenient, and cost-effective. Nanoparticles are being used to capture cancer biomarkers such as exosomes, circulating tumor cells, circulating tumor DNA, and cancer associated proteins for effective cancer diagnosis. The high surface area-to-volume ratio of nanoparticles in comparison to bulk materials is a key benefit for using them for cancer diagnosis. This characteristic allows for the dense coating of nanoparticle surfaces with antibodies, small molecules, peptides, aptamers, and other moieties to detect specific cancer molecules. Multivalent effects can also be achieved by exposing cancer cells to a variety of binding ligands, which can increase an assay's specificity and sensitivity.

Currently, chemotherapy, surgery, radiation, and a combination of these treatments are the most common methods of cancer treatment. However, these methods have significant drawbacks including, but not limited to, non-specificity and toxicity. The goal of modern medication is to optimize the pharmacological efficacy of drugs and minimize possible side effects. To avoid any unwanted responses, the drug's local concentration at cancer sites must be high, while its concentration in other tissues must be low. The application of nanotechnology in cancer treatment holds the potential to overcome the constraints of the conventional methods. Using nanotechnology, the amount of drug required to provide a therapeutic impact can be considerably lowered, and the drug concentration on the cancer site can be boosted without having any negative effects on healthy cells.

Several nanoparticle-based drug delivery systems such as nano-discs, high-density lipoprotein (HDL) nanostructures, gold nanoparticles, and viral nanoparticles have demonstrated promising outcomes in cancer therapy. Auspicious progress has been achieved in understanding the biological characteristics of cancer to improve the usage of nanoparticles by overcoming biological barriers and distinguishing between malignant and healthy tissues. Nano-drugs offer a lot of potential in cancer therapy because of their unique qualities such as limiting damage to healthy cells, overcoming multidrug resistance (MDR), and improving anti-cancer drug solubility.

Nanoparticles are used in medical applications because of their unique properties and due to their adsorption capacity to transport other compounds such as probes, proteins, and drugs.44 The composition of nanoparticles can be varied, just as starting materials can be biological lipids,45 dextran,46 lactic acid,47 phospholipids,48 chitosan,49 or chemicals such as silica,50 carbon,51 metals,52 and different polymers.12 Updating the available literature, summarizing new discussions, and adding new insights are very crucial to select the best options for cancer diagnosis and treatment. The main goal of this review is to summarize current advances in nanotechnology-based cancer diagnosis, therapeutics, and theragnostics. Further, current challenges and future perspectives are also discussed which could contribute to future studies working in the field.

Advantages and challenges of nanomaterial applications in cancer therapy:

Nanomaterials applied in cancer therapy have advantages over conventional chemical drugs as well as challenges in application. Several significant hallmarks in tumorigenesis and tumor development have been elucidated: continuous proliferative signaling, growth suppressors evasion, cell death resistance, replicative immortality, induced angiogenesis, activating invasion and metastasis, inflammation, genomic instability, and mutation. Traditional chemotherapy and radiotherapy have disadvantages in efficacy and side effects because of unspecific distribution and indiscriminate cytotoxicity to cancer cells and normal cells. Therefore, a delicate balance of dosing and an advanced targeting DDS is of great importance in cancer treatment. To reach cancerous target sites, chemical drugs taken orally or intravenously shall pass several "fortifications": TME and vasculature, MPS, BBB and kidney filtration. In physiological conditions, barriers like normal tissue microenvironment, vasculature, RES, BBB, and kidney filtration contribute significantly to pathogen resistance. However, in cancer treatment, intake of anticancer chemical drugs is affected by these defenses. Cancer cells hold a different proliferation pattern than normal cells. Cancer tissues exhibit distinctly in the dense extracellular matrix, over-activated angiogenesis induced by excessive angiogenic factors and high interstitial fluid.

Nanomaterial and drug metabolism:

Drug metabolism is a complex process. MPS, also called as reticuloendothelial system or macrophage system, consists of blood monocytes, tissue macrophages, and other immune cells. When dealing with extrinsic molecules, in this case, chemical drugs, parts of the MPS such as immune cells in the liver, spleen, or lungs will react, and activated macrophages or leukocytes quickly eliminate the drugs, causing short drug half-life. Nanocarriers with surface modification such as PEG or specific peptide possess lower MPS clearance and therefore prolong drug half-life. Kidney filtration is an essential function of the renal system. Renal clearance rate associates with several properties, including particle size, shape, and surface charge. For traditional chemical drugs, renal clearance is one of the key points needed in drug delivery. Proper renal clearance helps to minimize toxicity of nanocarrier. These barriers are obstacles for many conventional drug deliveries, diminishing drug efficacy in cancerous sites and indirectly increasing dosage and toxicity for normal tissue.

Nanomaterials and BBB:

The BBB is a highly specialized protection structure that protects the central nervous system from harmful agents and provides essential nutrition. BBB consists of brain capillary endothelial cells, which are arranged to form a "wall." Due to the blocking function of BBB, current post-surgery chemotherapy methods for brain cancer are mainly intraventricular or intracerebral direct injections, infusion, even implantation. However, these methods aiming at increased permeability might result in risks associated with high toxicity or inadequate drug distribution, that demands for a better solution to deliver anticancer drugs through BBB. In brain tumor treatment, conventional free chemical drugs are hard to reach cancerous sites through intravenous method due to BBB, and nanomaterials are researched to overcome this obstacle. EPR effect, peptide-modified endocytosis and transcytosis, focused ultrasound (FUS) are major approaches currently utilized to help deliver nanomaterials. Several nanomaterials have been researched for delivery through BBB, including NLCs, liposomes, and AuNPs.

Targeting strategies of nanomaterials applied to cancer therapy:

Targeted therapy aims at specific biological pathways or proteins that function in tumor growth. Molecules related to apoptosis and angiogenesis are also common targets in targeted therapies. Small molecules inhibitors and mAbs are two major tools to be utilized in targeted therapies. Through antigen–antibody conjugation, better specificity can be achieved. Compared with non-targeted therapies, free chemical drugs for example, targeted therapies specifically affect tumor-related molecular targets, while free chemical drugs kill both rapidly dividing normal cells and cancer cells. NPs loaded with targeted therapy drugs or modified with specifically targeted mAbs in the surface gain better efficacy and lower toxicity compared to nanocarriers loaded with anti-tumor chemical drugs.

Current challenges of nano-DDS designing:

Three key issues should be considered in anti-cancer nano-DDS designing: enhancement of efficacy, reduction of side effects, and resistance prevention. In many cases, a nano-DDS can solve several problems simultaneously due to instinct mechanism. A SLN synthesized with the material dexamethasone (Dexa)-conjugated lipid is linked with PEG-phosphatidylethanolamine (PEG-PE) and obtains Tf (transferrin)-PEG-PE ligands. As many cancer cells over-express the Tf receptor and use it to obtain certain molecular epitope, Tf is considered the target moiety that binds to the TfR molecular on the HepG2 cells. This kind of surface modification makes it a better delivery vehicle for gene, and the experiment shows that it displays remarkably higher transfection efficiency than both non-modified SLNs/pEGFP and vectors that do not contain Dexa in vitro or in vivo. The increased specificity results in higher drug accumulation in targeted cancer sites than other vital organs, leading to reduced toxicity and drug-related MDR prevention.

Applications of Nano Particles:

Nanomaterials used for cancer treatment

Polymeric nanoparticles

Nanoparticles are particles with size of nanoscale. Polymeric nanoparticles (PNPs), mAb nanoparticles, extracellular vesicles (EVs), metallic nanoparticles are broadly researched nanoparticles (NPs) . PNPs are defined as colloidal macromolecules with submicron size of 10–1000 nm. As drug carriers, PNPs carry chemical drugs and achieve the sustained release to targeted cancerous sites. Drugs are encapsulated or attached to the surface of nanoparticles thus forming a nano capsule or a nanosphere. The ingredients of nanoparticles have changed over the years. Initially, nonbiodegradable polymers such as polymethyl methacrylate (PMMA), polyacrylamide, polystyrene, and polyacrylates were used to fabricate nanoparticles. To avoid toxicity and chronic inflammation, polymeric nanoparticles made by these materials shall be cleared up in time. The accumulation of these types of polymer-based nanoparticles in tissues to a toxic level caused due to the difficulty to get them degraded, excreted, or physically removed have now been solved. Biodegradable polymers have been manufactured to reduce toxicity, improve drug release kinetic patterns, and increase

biocompatibility. These polymers include polylactic acid (PLA), poly(lactic-coglycolicacid) (PLGA), poly(amino acids) ,poly(ε-caprolactone) (PCL), and natural polymers consist chitosan, alginate, gelatin and albumin. These improved polymeric nanoparticles have special advantages due to their properties and structures. For volatile pharmaceutical agents, PNPs help increase stability. For chemical drugs, PNPs provide optional administration methods such as oral and intravenous and higher loading ability compared to free drugs. The ability that protects drugs from degradation helps minimize undesired toxicity to normal tissues; for instance, PNPs loaded with cisplatin such as dexamethasone or α-tocopheryl succinate have been employed in chemotherapy, which prevents cisplatin- induced ototoxicity.

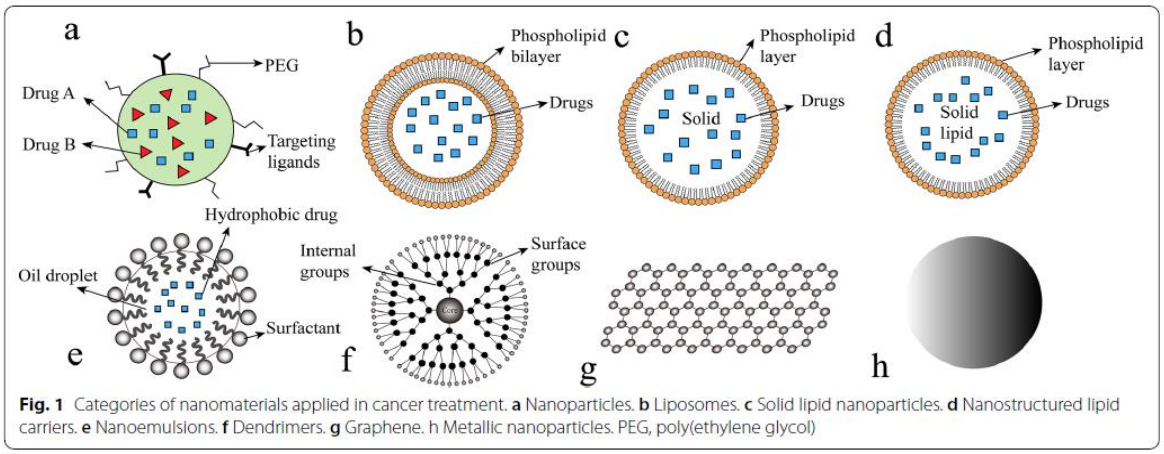

Fig. 1 Categories of nanomaterials applied in cancer treatment. **a** Nanoparticles. **b** Liposomes. **c** Solid lipid nanoparticles. **d** Nanostructured lipid carriers. **e** Nanoemulsions. **f** Dendrimers. **g** Graphene. h Metallic nanoparticles. PEG, poly(ethylene glycol)

Marketed NP for Cancer:

3.1.1 Doxorubicin (Doxil)

In 1995, the FDA-approved doxorubicin (Doxil), also known as Caelyx. It is a nanodrug used to treat multiple cancers, ranging from metastatic ovarian cancer to Kaposi sarcoma (KS) associated with AIDS. A doxorubicin (adriamycin) mixture is enclosed in unilamellar liposomes coated with PEG (polyethylene glycol) and are known as "PEGylated liposomes." The sizes of these structures vary between 80 and 90 nm. This DDS increases the half-life of circulation, leading to a boost in the bioavailability of medications. The first company to develop injectable Doxil was an Indian pharmaceutical company called Sun Pharma Global FZE, which obtained FDA approval in 2013.

3.1.2 Daunorubicin (DaunoXome)

Liposomal daunorubicin, commercially known as DaunoXome, was approved by the FDA in 1996. DaunoXome, another anthracycline drug, is used to treat cancer and HIV-associated Kaposi's sarcoma (KS). In addition, different clinical trials have demonstrated the applicability and efficacy of daunorubicin for various types of leukemia. Because of its potency and lower side effects compared with alternative cytotoxic drugs, such as adriamycin, bleomycin, and vincristine, DaunoXome has been approved as a first-line cytotoxic therapy in advanced KS. The liposomes have an approximate diameter of 45 nm and consist of cholesterol and distearoyl phosphatidylcholine compound lipid bilayers with a molar ratio of 1:2.

3.1.3 Irinotecan (Onivyde)

Onivyldan was approved by the FDA in 2015 as an irinotelatinoid nanoform (MM-398) derivative. Liposomal irinotecan has also been shown to exhibit synergistic effects with other anticancer agents. Irinosuccinate, 5-fluoracylinic acid, folinic acid, and oxalate folinamide treatment showed superior outcomes in patients with advanced pancreatic cancer. Nanoliposomal formulations have improved circulation time, passive tumor targeting, and fewer side effects due to tumor overexpression. However, there are still some side effects of Onivyde, including diarrhea, vomiting, stomach pain, and alopecia.

3.1.4 Cytarabine (DepoCyt)

DepoCyt was authorized under accelerated approval regulation in 1999. It is a cytarabine liposomal formulation that is produced using Depofoam technology. In 2007, the FDA approved it for the treatment of a life-threatening condition called lymphomatic meningitis. In this case, liposomal medicine was only delivered intrathecally into the spine. The liposomal formulation comprises dioleoyl phosphatidylcholine, dipalmitoyl phosphatidylglycerol, triolein, and cholesterol. This special liposomal preparation has a half-life 40 times longer than that of normal cytarabine.

3.1.5 Vincristine (Marqibo)

In 2012, the FDA-approved liposomal vincristine sulfate, also known as Marqibo. Vincristine is an alkaloid anticancer agent that binds to tubulin and interferes with the cell division. Marqibo is vincristine encapsulated in sphingomyelin/cholesterol liposomes

Patented NP for Cancer:

Table 3. Relevant patents on drug delivery mediated by nanoparticles.

Sr. No.	Patent No.	Classification	Patent/Publication Title	Inventor(s)	Organization	Issue/Publication Date
1	US 8,859,004 B2	Based on type of NP: *Polymeric*	pH-Sensitive Nanoparticles for Oral Insulin Delivery	Zhang L, Ling L, Zhou LY, Wu ZM, Guo XD, Jiang W, Luo Q, Qian Y	Nano and Advanced Materials Institute Limited, The Hong Kong University of Science and Technology, HK	Oct. 14, 2014
2	US 9,149,440 B2	Based on type of NP: *Polymeric*	Nanoparticles for Drug-Delivery	Turos E, Shim Jy	University of South Florida, US	Oct. 6, 2015
3	US 10,555,911 B2	Based on type of NP: *Polymeric*	Highly Penetrative Nanocarriers for Treatment of CNS Disease	Zhou J, Patel TR, Piepmeier JM, Saltzman WM	Yale University, US	Feb. 11, 2020
4	US 9,370,488 B2	Based on type of NP: *Lipid*	Method and System for Synthesizing Nanocarrier Based Long Acting Drug Delivery System for Insulin	Hamidi M	Kimia Zist Parsian (KZ); Tehran, IR	Jun. 21, 2016
5	WO 2018/031782 A 1	Based on type of NP: *Lipid*	Nanoparticle Compositions and Methods for Enhanced Stability and Delivery of Glycopeptide Drugs	Polt R, Heien ML, Pemberton JE	The Arizona Board of Regents on behalf of The University of Arizona	Feb. 15, 2018
6	WO 2013/176468 A1	Based on NP type: *Metallic (Gold)*	Liver Targeted Drug Delivery Systems Using Metal Nanoparticles and Preparing Method Thereof	Hahn SK, Lee MY, Yang J, Jung HS	Postech Academy Industry Foundation, KR	Nov. 28, 2013
7	WO 2014/047318 A1	Based on type of NP: *Metallic (Iron Oxide)*	Delivery of Therapeutic Compounds with Iron Oxide Nanoparticles	Kaittanis C, Grimm J	Memorial Sloan-Kettering Cancer Center, US	Mar. 27, 2014
8	US 10,456,363 B2	Based on type of NP: *Metallic (Iron Oxide)*	Modified Cyclodextrin Coated Magnetite Nanoparticles for Targeted Delivery of Hydrophobic Drugs	Joy P, Naduvilidam JK	Council of Scientific & Industrial Research, IN	Oct. 29, 2019
9	WO 2018/102921 A1	Based on type of NP: *Metallic (Gold)*	Ultrastable Gold Nanoparticles for Drug Delivery Applications and Synthesis Thereof	Boisselier E, Ouellette M, Pernet V, Omar M	Universite Laval, CA	Jun. 14, 2018
10	US 8,535,726 B2	Based on type of NP: *Carbon*	Supramolecular Functionalization of Graphitic Nanoparticles for Drug Delivery	Dai H, Liu Z, Li X, Sun X	The Board of Trustees of the Leland Stanford Junior University, US	Sep. 17, 2013
11	WO 2014/015334 A1	Based on NP type: *Carbon*	System and Methods for Nanostructure Protected Delivery of Treatment Agent and Selective Release Thereof	Wu CH, Kim JH, Xu J	Brown University, US	Jan. 23, 2014

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