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MAGNETIC NANOPARTICLES IN CANCER TREATMENT: A REVIEW

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ABSTRACT

Magnetic nanoparticles have made significant strides in oncology in recent years. The intrinsic magnetic property of MNPs makes them the most promising nanomaterial to be used as contrast agents for magnetic resonance imaging and induced magnetic hyperthermia. General nanoparticles are widely used in tumor targeting. When MNPs are employed as drug delivery agents, their properties are fully utilized. By applying an external magnetic field, drugs can be directed to the precise location that is desired in vivo. Since MRI can help with early cancer diagnosis, it may be used in conjunction with customized treatment to provide the right diagnosis and course of action. A diagnosis of cancer early detection of cancer significantly increases the cure rate. Therefore, lowering the patient mortality rate requires early cancer detection and prompt diagnosis. The diagnosis of cancer and the selection of late-generation magnetomotive photoacoustic technology with cyclic magnetic motion and ultrasound speckle tracking are crucial applications of tumor imaging technology. This technology's imaging capture frame rate is several hundred times faster than that of the previously proven photoacoustic speckle tracking method. Using NIR imaging, Stone et al. showed a magnetic NP system that could be used to monitor the NP fate inside a biofilm diagnosis, medication delivery, and treatment has been compiled in this review. Also covered are the prospects and difficulties facing MNPs in the field of oncology in the future.

KEYWORDS: Drug Delivery, Cancer, Magnetic Nanoparticles, Cancer Diagnosis.

INTRODUCTION

With their small particle size, large specific surface area, magnetic response, and superparamagnetism, magnetic nanoparticles [MNPs] are a type of intelligent nano-

magnetic material [1]. The electromagnetic wave in the alternating magnetic field absorbs the heat when MNPs are assembled and placed in a continuous magnetic field. MNPs are typically found in the superparamagnetic state in biomedical applications [2,3]. Iron oxide nanoparticles, such as magnetite [Fe3O4] and maghemite [γ-Fe2O3], are the most commonly used nanomaterials [4]. MNPs are known to play a significant role in the diagnosis, delivery, and treatment of cancer. Tumor imaging technology made early disease detection possible for the diagnosis of cancer. Magnetic resonance imaging [MRI] [5], computed tomography [CT] [7], magneto acoustic tomography [MAT] [6], and near-infrared [NIR] imaging [8] are examples of common imaging modalities. Superparamagnetic iron oxide nanoparticles, or SPIONs, are the most representative contrast agent for MRI among them, and MRI plays a significant role in the early diagnosis of cancer [9]. Some iron oxide-based MNPs are currently authorized for use in clinical MRI; for instance, ferumoxil [Gastro MARK] improves bowel imaging [10]. MNPs can easily reach the lesion site because of their small size and large specific surface area [11]. Consequently, it is impossible to overlook the use of MNPs as drug carriers for drug delivery. When used as drug delivery agents, MNPs' ability to target drugs to a specific location in vivo through the application of an external magnetic field is fully utilized [12]. MNPs typically bind to chemotherapeutic drugs [14], as well as antibodies [13] to serve as drug carriers. MNPs are frequently loaded with chemotherapeutic medications, which are used to treat cancer. Chemotherapy, magnetic hyperthermia [MHT] [15], photodynamic therapy [PDT] [16], and photothermal therapy [PTT] [17] are the main ways that MNPs are used in the field of cancer therapy. Combination therapy is typically employed to improve the therapeutic effect. A framework for the use of MNPs in medicine, including cancer diagnosis, medication delivery, and treatment, is presented in this review. Along with the possible difficulties and opportunities, nanotoxicity is also reviewed.

1.The diagnosis of cancer

Early cancer detection significantly increases the chance of recovery. Therefore, the key to lowering the patient mortality rate is early detection and prompt diagnosis of cancer [18]. The decision to use a late-generation magneto motive photoacoustic with cyclic magnetic motion and ultrasound speckle tracking, whose imaging capture frame rate is several hundred times faster than the previously proven photoacoustic speckle tracking method, is crucial for the diagnosis of cancer. In order to use NIR imaging to observe the NP fate within a biofilm, Stone et al. demonstrated a magnetic NP system.Furthermore, using a mouse model of orthotopic mammary cancer, Xi et al. [27] demonstrated a breast imaging method that combines high-resolution NIR light-induced photoacoustic tomography [PAT] with NIR dye-labeled amino-terminal fragments of urokinase plasminogen activator receptor-targeted magnetic iron oxide NPs [NIR830-ATF-IONP] for breast cancer imaging. MPI [29] and ultrashort echo time [UTE] imaging [28] have been shown in other studies to potentially enhance the detection of MNPs in cancer. Other imaging techniques are combined with MRI for MNPs. This dual imaging technique could increase diagnosis accuracy. For example, pancreatic and breast [30] cancers have been treated with dual imaging using single-

photon emission computed tomography [SPECT] and magnetic resonance imaging [MRI]. The synthesis and application of monodisperse iron oxide nanoparticles coated with fluorescent silica nanoshells for fluorescence and magnetic resonance dual imaging of tumors were demonstrated in a study by Jang e [31]. Additionally, Sun et al. [32] used optical imaging [OI] and magnetic resonance imaging [MRI] to diagnose breast cancer.

Pancreatic imaging position

Because of its late presentation, pancreatic cancer is one of the most deadly cancers worldwide [33]. Consequently, patients will have a higher chance of recovery with an early diagnosis. Survivin antisense oligonucleotides [ASON] and chitosan-coated MNPs are conjugated to produce Sur-MNPs, which function in tandem with ASON to cause targeted localization in pancreatic tumors [34]. Pancreatic tumors could be detected by MRI using survivin-targeted NPs. Biodegradable NPs were created using recombinant human serum albumin and iron oxide [maghemite, γ-Fe2O3], taking into consideration the more sensitive diagnostic tools to enable early medical imaging. SPECT-CT and MRI showed improved imaging and targeting capabilities in mice.

Imaging techniques

MRI

MRI has been regarded as one of the most valuable noninvasive imaging techniques due to its high spatial resolution and tomographic capabilities [19], and MNPs have recently been proposed as an alternative to MRI [20]. Generally speaking, conducting surface modification of nanoparticles [NPs] by inducing the magnetic dipole interaction and its intrinsic surface energy is required to overcome the colloidal instability of MNPs. PEGylated folic acid [FA] and fluoresce in isothiocyanate [FI] were successively added to water-dispersible polyethylene imine [PEI]-coated Fe3O4 nanoparticles [NPs] through PEI-mediated conjugation chemistry [21]. The colloidally stable FA-functionalized Fe3O4 NPs for MRI were created by acetylating the remaining PEI surface amines. In MRI, studies have shown that sensitive imaging of superparamagnetic NPs or aggregates may detect early lesions in a 6-year-old boy with glioblastoma multiforme [22]. Additionally, the study showed that the multifunctional nanocomposites showed promise for combining diagnostic and therapeutic properties [23].

Additional imaging techniques

According to a study by Mariappan, magneto acoustic tomography estimates an image of the distribution of the NPs in vivo with ultrasound imaging resolution by using a short pulsed magnetic field to induce ultrasound in tissue that has been SPION-labeled. High spatial resolution and sensitivity are made possible by magnetic particle imaging [MPI], a technique similar to atomographic imaging. According to a study by Lindeman et al. [24] University of Luebeck Dextran-coated SPIONs are promising tracer materials for use in novel tumor cell analysis in MPI. Additionally, as a potential imaging tool, photoacoustic imaging has drawn more attention. A study by Lietal [25–34] created a new.

The breast

Some guidelines for designing a the imaging device for MNPs to improve the microwave imaging of breast cancer were outlined in a study by Bucci et al. [35]. The findings showed that, when designed in accordance with the established guidelines, MNP-enhanced microwave imaging may accurately detect cancer lesions even with low-complexity arrangements. According to a study by Kato et al [36], liposome encapsulation greatly enhanced the delivery and retention of SPIONs in breast tumors. Targeted SPION liposomes also significantly enhanced accumulation in breast tumors, making them potentially the best choice for MRI breast tumor detection. Sun et al demonstrated that more peptide cyclic-arginine-glycine-aspartic acid [RGD]-FMNPs accumulated around the tumors than FMNPs when magnetic nanoclusters coated with ruthenium [II] complexes doped with silica [fluorescent magnetic nanoparticles, or FMNPs] were used. The findings suggested that RGD-FMNPs could be used as a targeting molecular probe for MRI and OI-based breast cancer detection. Bevacqua and Scapaticci [37] used a compressive sensing technique for three-dimensional breast cancer in order to make a more precise and targeted diagnosis of the disease.

The prostate

MRI is the recommended imaging modality for patients with prostate cancer because it offers the best soft tissue resolution and plays a significant role in the management of prostate cancer [38]. After injecting radiolabeled tracers, lympho scintigraphy is frequently used to evaluate the sentinelly lymph node [SLN] in patients with prostate cancer. For instance, patients used T1-, T2-, and T2*-weighted sequences for MRI at 1.5T before and 1 day after SPION injection. This was the first study to visualize SLNs by MRI in patients with prostate cancer using intraprostatic injection of SPIONs [39]. According to a study by Winter et al. [40], it is safe, practicable, and consistently detects lymph node metastases and SLNs in the majority of patients when SPIONs are injected transrectally intraprostatically for magnetic marking in prostate cancer. In other situations, the Gleason score, a histological indicator of prostate cancer aggressiveness, correlates with the sensitivity of diffusion-weighted [DW] MRI to water diffusion throughout tissues [41].

Lung

Wan et al. [42] developed immune SPIONs for use in magnetic resonance immune imaging to increase the sensitivity of lung cancer metastasis detection. After coating these SPIONs with carboxymethyl dextran and oleic acid, they were conjugated to a mouse anti-cluster of differentiation [CD]44v6 monoclonal antibody. Lung tumor-targeting diagnosis may benefit from the prepared SPIONs. Additionally, targeted pulmonary inhalation aerosol-based delivery has inherent benefits and makes it easier to administer medications directly to the lungs in a controlled manner [43]. Therefore, using small animal experiments, Nishimo et al. [46–52] examined the viability of applying MPI to pulmonary imaging using nebulized MNPs and to quantify the mucociliary clearance in the lung [53-55].

Other

The prostate, breast, and pancreas are commonly treated with common contrast agents. In other situations, a range of imaging modalities are used in conjunction with the diagnosis and treatment, as described in.

Delivery of drugs

Magnetically targeted drug delivery has been used to decrease side effects and enhance the therapeutic efficacy of medications used in traditional cancer treatment. MNPs with a stabilizing shell coating have been effectively employed as MRI contrast agents [56]. Early diagnosis may allow for simultaneous treatment, which could significantly increase efficiency. MNPs are therefore crucial to drug delivery. MNPs can be employed as drug carriers by binding antibodies, chemotherapy, or other medications.

Antibodies

Because of their high-level accumulation within cancer cells, research has shown that antibody-conjugated MNPs may be used to treat ovarian cancer in addition to detecting ovarian cancer biomarkers [57,58]. For the first time, a study by Wang et al. revealed that HAI-178 monoclonal antibody [mAb] conjugated fluorescent MNPs, an anti-α subunit of adenosine triphosphate synthase antibody, was successfully used for targeted imaging and simultaneous therapy of invivogastric cancer. Regarding human breast cancer, Shanehsazzadeh et al [59] showed disappointing in vivo results when conjugating ultra-small SPIONs with C595 mAb, with very little accumulation of nanoprobes in the targeted site. In contrast, a study by Rasaneh and Dadras [60] proposed that combining MNPs with a permanent magnet could improve the therapeutic efficacy of herceptin for greater accumulation in the tumor site. Combining antibodies with chemotherapeutic medications is becoming more and more popular as a way to increase therapeutic efficacy. A new multifunctionalized iron oxide MNP with anti-CD44 antibody and gemcitabine derivatives was presented in a study by Aires et al. [61] along with their use for the selective treatment of CD44-positive cancer cells. Furthermore, Huangtal [62] created a novel cancer dual-targeting treatment that uses magnetic Fe3O4 nanoparticles grafted with single-chain antibodies and β-cyclodextrin loaded with docetaxel. These studies have shown how effective the combination of chemotherapeutic medications and antibodies can be.

Chemotherapy medication

As listed in Table II, common chemotherapy medications include doxorubicin [DOX], paclitaxel, cisplatin, gemcitabine, methotrexate, docetaxel, and sorafenibandmitomycin C. The most commonly used chemotherapy medication in targeted delivery systems is DOX [63]. MNPs' stability is limited due to their hydrophobic coating [64]. A reducible copolymer self-assembled with SPIONs was created to deliver DOX for cancer treatment in order to address this problem [14]. Michael addition was used to create the copolymer of reducible polyamidoamine with polyethylene glycol/dodecyl amine graft [14]. Furthermore, studies have shown that the use of iron oxide MNPs enhanced DOX-NP cell penetration in comparison to free

DOX and produced an acellular response to DOX-NP conjugates that was comparable to that of DOX alone [65]. Additionally, SPIONs have been studied as a targeted drug delivery vehicle. For instance, Chichaetal [66–75] established an in vitro system to examine the various facets of cellular reactions to mitoxantrone-carrying [76–84].

Other

Some traditional Chinese medicine products have been used as anti-cancer medications in targeted drug delivery in addition to chemotherapy drugs. The fabrication and characterization of dendrimerized MNPs as epigallocate-echingallate delivery vectors were presented in a study by Nigam and Bahadur [85]. Curcumin has recently been widely used in the drug delivery of MNPs in breast cancer. In a study by Mancarella et al. [86], Fe3O4 NPs were functionalized layer by layer by coating them in Dextran and Poly[L-lysine], which resulted in a high upload of curcumin in Fe3O4 NPs for the treatment of ovarian cancer. Additionally, it has been shown that magnetic Fe3O4@hydroxyapatite-PEI-b-cyclodextrin NPs and magnetic Fe3O4@zirconium phosphate core-shell NPs are efficient drug carriers for the delivery of curcumin, and both have been used to treat breast cancer [87,88]. In other situations, oligonucleotides are used in drug delivery. In a study by Pourianazar and Gunduz [89], they used three-layer MNPs made of a cationic poly [amidoamine] dendrimer, an aminosilane interlayer, and a Fe3O4 magnetic core to improve the accumulation of CpG oligodeoxynucleotide molecules in tumor cells as a novel targeted delivery system. Additionally, 2-amino-2-deoxyglucose was conjugated to COOH-modified cobalt ferrite MNPs, which were intended to target tumor cells as a possible targetable drug/gene delivery agent for the treatment of cancer [90]. In conclusion, MNPs might offer a highly effective drug delivery method that could lead to drug targeting.

Treatment for cancer

The ultimate objective of MNPs as drug carriers is to treat. This section discusses and provides examples of the use of MNPs in MHT, PDT, PTT and combined treatment.

MHT

Because of its possible medical applications, MHT has garnered a lot of attention lately. Electromagnetic energy can be transformed into heat by MNPs [91]. Thus, heating tumor cells to their apoptosis threshold is probably the most common use for MNPs [92]. Important factors that may increase the effectiveness of heat generation for cancer therapy at low NP treatment doses include magnetic field strength and frequency, NP size, NP concentration, and solution viscosity [93]. The in vivo anti-tumor effect under a low-frequency magnetic field using MNPs has not yet been demonstrated, despite the fact that MNPs represent an area of active development for MHT.

The in vivo anti-tumor effect under a low-frequency magnetic field using MNPs has not yet been demonstrated, despite the fact that MNPs represent an area of active development for MHT. A study by Cheng et al. [94] showed that glioma cells could be successfully destroyed in vitro and in vivo using spin-vortex, disk-shaped permalloymagnetic particles in a low-frequency, rotating magnetic field. Furthermore,

hysteresis loss is crucial for MHT since it improves heating efficiency [94]. The hysteresis loss of magneti-cally fractionated MNPs for use in hyperthermia was investigated in a study by Sasayama et al. [95]. They came to the conclusion that magnetically separating MNPs increases the efficiency of hyperthermia [95]. In general, MHT may somewhat increase the effectiveness of chemotherapeutic medications. For example, the therapeutic effects of MHT in breast cancer could be significantly increased by combining SPIONs [MF66] that are functionalized with Nucant multivalent pseudopeptide [N6L], DOX, and MHT [96]. Additionally, dual-functional Pt-Fe-hydroxyapatite MNPs were created for the treatment of lung cancer by chemo-hyperthermia [97]. Furthermore, studies have shown that MHT of MNPs improved radiation treatment in human prostate cancer murine models [98]. In other situations, gene delivery plays a significant part in MHT as well [99,100].

PDT

PDT is a minimally invasive, externally activated cancer treatment method. Photosensitizing drugs, also known as photosensitizers [PSs], are applied either locally or systemically as part of the PDT process. The PSs are then photoexcited in the tissue using light of the proper wavelength and power. When oxygen is present, the PS is excited from its ground state to its excited state after being activated by light of the proper wavelength. An electron is then transferred to the oxygen in the surrounding tissue, creating excited single oxygen or oxygen free radicals. These chemicals, also referred to as reactive oxygen species [ROS], harm cells and eventually cause tissue damage in cancer. Building a targeted drug delivery system with MNPs has gained attention as a way to increase the impact of PSs. For example, Park et al. synthesized multifunctional cobalt ferrite [CoFe2O4] nanoparticles [NPs] [CoFe2O4-hematoporphyrins [HPs]-FAs] and functionalized them by conjugating with FA to target cancer cells and coating them with HP to introduce photo-functionality. Additionally, other studies have shown that the Fe3O4@HP particles showed strong anti-cancer effects on human prostate cancer [PC-3] and breast cancer [MDA-MB-231] cell lines, as well as remarkable and effective photodynamic anticancer activity. For PDT, pyrophorbide-a [PPA] as anovelchlorin PS was prepared. Fe3O4@SiO2@ CS@PPA [MFCSPPA], a PPA-coated multifunctional magneto-fluorescent nanoparticle, was designed. The experiments showed that MFCSPPA had low dark toxicity and strong photodynamic therapy activity. After receiving PDT, the cell viability of human HeLa cervical cancer cells dropped to 18%.

PTT

Because of its light toxicity to the skin and deep tissue penetration, NIR may kill cancer cells directly by PTT, which is now a controlled treatment method. PTT, which uses photothermalagents in conjunction with NIR, has also drawn more attention as a cancer treatment option. Engineering phosphopeptide-decorated MNPs as effective photothermal agents for solid tumor therapy is one example of this. Notably, the photothermal effect of MNP clusters was first documented for the in vivo and in vitro photothermal ablation [PTA] of tumors. Clustered Fe3O4 NPs may lead to a significant increase in NIR absorption when compared to individual magnetic Fe3O4

NPs. Clustered Fe3O4NPs that produced higher temperatures upon NIR irradiation at 808 nm were more cytotoxic to A549 cells. PTT and MRI are typically performed in tandem. But according to a study, small Fe3O4 NPs showed more cellular internalization than their large counterparts, which allowed for a higher PTA efficacy in vitro. Furthermore, the ideal diameter of Fe3O4 NPs for MRI and PAT in vitro may be nm. As a result, MNP size may be a significant PTT factor.

Combination Therapy

MNPs typically serve as drug carriers for systems of targeted delivery. For combined cancer PTT and PDT, the nanocomplex containing PSs and PTT agents may be utilized. The first use of magnetic-optical hybrid nanosystems for dual mode PTT and PDT and magnetic-field-guided drug delivery was shown in a study by Bhana et al. Under NIR laser irradiation, the composite NPs may produce heat and ROS concurrently, and they may even be delivered to the mitochondria specifically. Moreover, MNPs have been shown to have the dual ability to enhance heating efficiency by acting as both magnetic and PTT agents. In summary, these findings showed a significant accumulation of MNPs in superior

APPLICATIONS

Other groups have created and improved magnetic micro- and nanoparticle-based drug and gene delivery systems since the work of Widder and others, with differing degrees of success. Doxor-ubicin was coupled to magnetic particles and targeted to sarcomatumors implanted in rats in the first study by Widder and others, and the method has proven successful in a number of animal studies. The control group, which received ten times the dosage but no magnetic targeting, showed no signs of remission, while the magnetic-targeting group experienced complete remission. Numerous other animal studies, not just involving small animals, have reported tumor remission. such as rats and rabbits [e.g., Alexio Pulfer], but also larger pigs, and one study had increased the targeting depth to about 10 cm. Recently, Alexiou and colleagues used HPLC analysis of mitoxantrone bound to ferrofluids to successfully quantify the distribution of magnetically targeted carriers in a rabbit model. They also used light microscopy to show that magnetically targeted carriers are absorbed in HeLa cells in vitro. Kubo and others installed permanent magnets at solid osteosarcoma sites in hamsters, followed by the delivery of cytotoxic compounds via magnetoliposomes, in an attempt to address issues with the spatial configuration of these delivery systems. Compared to standard intravenous [non-magnetic] delivery, this led to a fourfold increase in drug delivery to the tumor site. The group also reported a significant increase in anti-tumor activity and a decrease in side effects related to weight loss. Another possible solution to the geometry problem is suggested by theoretical and experimental analysis of implanted magnetic grids for targeting the heart muscle. Despite two Phase I/II clinical trials, the use of magnetic targeting in humans has not yet reached the market. Lu¨bbe and others conducted a Phase I clinical trial on 14 patients. Although targeting was examined in detail, particle accumulation was seen in the tumor masses of six of the patients. This was primarily done to assess the potential toxicity of the particle-carrier complex. The study showed

that magnetic carriers are generally well tolerated, even though the particles accumulated in the heliver.

Magnetic Nanoparticles/Carriers

There are a number of methods for creating magnetic nanoparticles for drug delivery. It is possible to produce particles with a core-shell structure, in which the core is a magnetic iron oxide [typically magnetite [Fe3O4] or maghemite [gFe2O3]], and the shell is typically a polymer like silica, dextran, or PVA, or metals like gold to which functional groups can be attached via cross. Both ionic and non-ionic surfactant techniques can be used to synthesize this kind of structure, or it can be encapsulated within a structure like a carbon cage or ferritin protein [for example, see Meldrum et al., Carboxyl groups, amines, biotin, streptavidin, antibodies, and other substances can then be attached to these particles to functionalize them.
Several groups have created methods for the synthesis of magnetoliposomes in addition to these polymers. These nanoparticles have an unusual core-shell structure, with an artificial liposome encircling a magnetic iron oxide core. These are typically used to treat magnetic hyperthermia, but they could also be helpful for drug delivery. Additionally, particles can be incorporated into hydrogels to carry a therapeutic agent that is released upon heating, or the particles themselves can be used for applications involving hyperthermia. Lao and Ramanujan, Chenetal More recently, 5–25 nm-sized gold/cobalt nanoparticles with a core-shell structure and a customizable shape have been created. The rapid breakdown of organic precursors in the presence of surfactants, which regulate the particles' size and shape, has produced these particles. One of these particles' main advantages is that cobalt has a magnetic moment that is almost twice as high as that of magnetite or maghemite. The precipitation of magnetic iron oxide nanoparticles within an aporous polymer micro-ornanoparticle scaffold is another method for creating magnetic/polymer nanoparticles. One benefit of this technique is that it makes it possible to create particles with a well-defined, spherical shape and a relatively tight size distribution. As with core-shell structures, the particles can be functionalized to allow for the attachment of drugs or the embedding of therapeutic compounds within a biodegradable polymer.

CONCLUSION

As imaging contrast agents, MNPs have a lot of promise for adjuvant treatment. However, numerous limitations have been placed on the use of MNPs because of the toxicity that has been linked to their use. It is well known that MNP surface coatings affect both the beneficial properties and possible toxicity of MNPs. Studies have shown that the accumulation in vivo increases with the size of the MNPs. Consequently, regulating MNPs' surface coatings and size may lessen toxicity and enhance their magnetic properties. In this review, we concentrated on MNP-assisted drug delivery, cancer diagnosis through imaging, and cancer treatment. There are still certain difficulties even after numerous successful studies employing MNPs as a catheter-like substance. Even though a lot of MNP formulations have shown great results in small animal models, they fall short of the clinical standard. MNPs may be able to be used clinically with integrated imaging and multimodal therapy in the near

future and have a significant impact on cancer treatment if their drug loading capacity is improved and their specificity and affinity to target cancer cells are increased.

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