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Review Article

MAGNETIC NANOPARTICLE-BASED APPROACHES IN CANCER THERAPY–A CRITICAL REVIEW

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ABSTRACT

Cancer is definitely one of the leading causes of mortality worldwide. Failure in the efficacy of the standard treatments (chemo-, radiotherapy and surgery), and the severe side effects, resistance of tumor cells to chemotherapeutics have necessitated alternative therapeutic strategies. Magnetic nanoparticles (MNPs) have been assessed as potential cancer therapy materials. Their intrinsic magnetic properties provide a cancer detection, monitoring, and therapy platform based on multimodal theranostics. MNPs can be functionalized by binding them to a wide variety of substances, including chemotherapeutic drugs, radionuclides, nucleic acids, and antibodies. They can be used for drug delivery, magnetic or photothermal induced local hyperthermia and photodynamic therapy aimed at killing cancer cells at the tumor site. MNPs may also be useful to challenge drug resistance. The combination of different options of these treatment modalities offers a synergistic effect and significantly reduces the side effects. The functionalized MNPs may be used to remove the unwanted cells from blood, including leukemia cells and circulating tumor cells that key factors in the metastatic process. Despite numerous successful studies, there are still some unpredictable obstacles relevant to the use of MNPs in cancer therapy. This review mainly focuses on the application of MNPs in cancer treatment, covering future perspectives and challenges aspects.

Keywords: Cancer therapy, Magnetic nanoparticles (MNPs), Functionalization, Drug delivery, Hyperthermia, Combination therapy

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INTRODUCTION

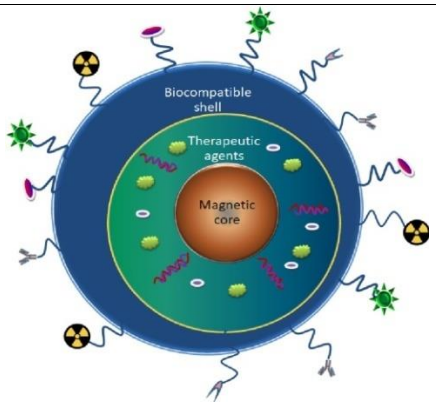
Cancer is one of the leading causes of death globally and an important barrier to increasing life expectancy of man. It is estimated that 19.3 million new cases and 10.0 million cancer-related deaths worldwide occurred in 2020 [1]. Successive mutations that may occur in the oncogenes, tumor suppressor genes and DNA repair genes due to various reasons trigger the development of the cancer cell. There is also an important struggle between the body's immune system and cancer development. This struggle consists of a three-stage process called "cancer immunoediting", and can be specified with 3E, including phases of elimination (immune system's initial response to tumor), equilibrium (immune-mediated tumor dormancy), and escape (tumor evasion of immunological response) phases [2].

In addition to the failure in the standard treatments (chemo-, radiotherapy and surgery), their effectiveness remains limited because of the resistance of tumor cells to chemotherapeutics, the suppression of the immune system, dose-related toxicities, and other major side effects. As a result, there is a pressing need to conceive and develop new therapeutic strategies [3]. As one of the alternatives, nanotechnology presents a new frontier in cancer treatment. The use of nanoparticle (NP) carriers as effective drug delivery systems encourage studying therapeutic researches for cancers [4]. Functionalized and targeted NPs could benefit from differentially receptors expressed by tumor cells and contribute effective and sustained release of anticancer bio-actives. NPs can be directed into the diseased parts; consequently, they both improve the efficacies of therapeutics and reduce systemic toxicity [5].

Fig. 1: Ideal characteristics of a nano-based targeted drug delivery system [6]

Magnetic medication targeting, in which magnetic nanoparticles (MNPs) play a role, is an alternative and relatively new cancer treatment approach. MNPs are nanomaterials with diameters ranging from 1 to 100 nm that may be guided to cancerous tissues using an external magnetic field (EMF) [7]. These nanoparticles have a lot of potential in a range of applications because of their intrinsic magnetic capabilities and multifunctional design, such as a multimodal theranostics platform for cancer diagnosis, monitoring, and therapy [8]. In addition to their directly anti-cancer properties, MNPs may be gained biocompatible characters by coating and imparted highly-functionalizable by loading some molecules such as drugs, radioactive agents, genes, targeting ligands/antibodies and imaging objects (fig. 2). According to the usage aim, the loading may be alone or in combination forms consisting of two or more choices [9].

This review aims to focus on usage of the MNPs in cancer treatment. A more detailed overview has been provided about the properties of MNPs, their functionalization, and therapeutic applications including drug delivery, magnetic hyperthermia, and photodynamic therapy. In addition to it, the toxicity, pharmacokinetics, and bio-distribution of MNPs and future perspectives and challenges in regarding to the therapeutic applications have been briefly highlighted. This literature survey was done in PubMed, Cochrane library and the keywords used to search were magnetic nanoparticles, types, functionalization and cancer. The review is a complete collection of articles from the last 10 y (from 2010 to 2021).



Symbol	Characteristic	Function
	Ligand	Binding to target
	Antibody	Binding to target/Immunotherapy
	Chemotherapeutic drug 1	Chemotherapy
	Chemotherapeutic drug 2	Chemotherapy
	Therapeutic protein	Therapeutic effect
	Radioactive substance	Radiotherapy
	Nucleic acid	Gene therapy
	Fluorescent molecule	Detection of localization
	Linker	Link the molecules to MNP

Fig. 2: Schematic depiction of a multifunctional biocompatible structure of shell coated MNP-loaded with different types of targeting ligands, therapeutic substances and imaging agents. Therapeutic drugs can be conjugated on the surface or embedded in the coating (modified from [9])

Synthesis and characterization of MNPs in cancer therapy

MNPs are generally composed of magnetic elements and their chemical compounds such as iron, nickel, and cobalt. Contingent on their chemical composition, MNPs can be undisclosed simply as iron oxides (ferrites) and metals containing only metallic core and their coated forms.

The method of synthesis and chemical structure of MNPs affect their physical properties. Magnetic iron oxide (usually maghemite γ-Fe_2O_3 or magnetite Fe_3O_4) are the greatest widely investigated MNP since iron is believed to be more biocompatible. This kind of the MNPs used in biomedical claims frequently contain of one or more magnetic iron-ore or maghemite cores and with biocompatible shell functionalized with various transformers. They are called as superparamagnetic iron oxide nanoparticles (SPIONs) [10, 11].

Size, shape, and surface charge of the MNPs affect their effectiveness. Wang *et al.* employed rod-shaped magnetic mesoporous silica-based nanoparticles (MSNs) in hepatocellular cancer suicide gene therapy. Compared with sphere-like MSNs, they demonstrated that rod-like MSNs, exhibited higher loading capacity, faster prodrug release rate, stronger magnetically enhanced and effective gene delivery and better magnetic hyperthermia properties [12].

These nanomaterials can be synthesized by organic-based (e. g., polymeric nanoparticles, magneto liposomes, micelles or ferrogels) and inorganic based (e. g., gold or mesoporous silica) materials [13]. MNPs can be tuned for multiple cancer therapy applications. Their surface coatings and their functionality increase colloidal stability, improve biocompatibility, facilitate transport to target tissues/cells, and allow covalent or electrostatic attachment of therapeutic and targeting fragments to the cargos, and also reduce side effects such as internal toxicity and immunogenicity [14]. Polyglycerol (PG) coating, which is a biocompatible polymer and has a chain structure similar to that of polyethylene glycol (PEG), ensures optimum hydrophilicity, constancy, and confrontation to non-specific protein adsorption in the vivo environment [15].

There are many situations in which drug release particles targeting cancer have to be overcome. To overcome these problems, MNPs can also be engineered to modulate drug release by a range of stimuli, including as pH, magnetic field, and internal stimuli like hypoxia-sensitive delivery [3]. To capture the therapeutic drug particles and their releasing in a controlled manner can be ensured by using temperature-, hypoxia-or pH-sensitive materials for their synthesis and applying an EMF [10].

Administration, pharmacokinetics, biodistribution, the toxicity of MNPs

MNPs' route of management, toxicity, pharmacokinetics, and biodistribution structures are all serious for successful cancer therapeutic applications. Depending on the purpose and the target structure, there are several routes of MNPs administration such as parenteral, directly intra-tumoral, oral or nasal. Depending on the administration route, clearance of the MNPs from the bloodstream by metabolism and excretion might be a problem [16]. The size of MNPs has an important influence in their pharmacokinetics and biodistribution within the body. Smaller particles (less than 10 nm) are clean out more rapidly by renal clearance, while bigger particles (greater than 200 nm) are disqualified by the hepatobiliary pathway after sequestration in the spleen and liver [3]. The surface coating of MNPs also has a substantial impact on their biodistribution and biocompatibility. These are crucial considerations in the *in vivo* applications of MNPs [17].

Drug access into the targeted area can be through passive or active ways. In the passive way, the disrupted vascular barrier at tumor sites allows NPs to accumulate in the tumor tissue. Moreover, the NPs are not rapidly cleared due to poor lymphatic function and they accumulate in the tumor interstitium. This called as enhanced permeability and retention (EPR) effect [18].

The active targeting involves affinity-based recognition, retention and facilitated uptake by the targeted cells. This is also known as the ligand-mediated targeted approach. These NPs are internalized by

the cells through endocytosis or phagocytosis. Target substrates can be founded on receptors that are ended-or solely expressed by tumor cells, or additional over-expressed class such as low molecular weight ligands (folic acid, thiamine, sugars), proteins (transferrin, antibodies, lectins), peptides, polysaccharides and DNA etc. Then, antibodies, lectins, proteins, hormones, charged molecules and low molecular weight ligands (e. g. folate) are the biomolecules most frequently used as ligands [7]. In the active targeting, MNP can be guided by means of a magnetic field. Furthermore, binding of one ligand molecule generally facilitates binding of other molecules conjugated the NP to their specific targets, which result in considerably increased cumulative effects [18].

MNPs can cause toxicity through a variety of mechanisms, the most common of which is the formation of reactive oxygen species (ROS). MNP surfaces can be changed to allow therapeutic compounds to accumulate passively or actively at target areas with minimal systemic toxicity. The combined medicines lower toxicity while enhancing synergistic effects [7]. In order to achieve the best results, there are still many important factors to overcome, such as optimizing the density of ligands to be conjugated to MNPs and evaluating the toxicity [16].

Cancer therapy using attractive nanoparticles

MNPs take newly donated to significant development in the field of oncology. In calculation to direct use of MNPs on the foundation of killing cancer cells, there are various therapy approaches utilizing nanoparticles, due to their intrinsic qualities, such as photothermal therapy (PTT), photodynamic therapy (PDT), magnetic hyperthermia therapy (MHT), administration of chemo-, radio-, and immunotherapeutic agents, bi-/three-modal or other therapy strategies These therapy approaches, particularly multimodal therapy consisting of simultaneous hyperthermia and chemotherapy (CT), can upsurge the efficiency of the action while dipping unsought side properties [19, 20].

MNPs as cargo delivery vehicle

Drug delivery

MNPs can be loaded with a high amount of active substances thanks to their large surface/volume ratio. They are considered ideal candidates for controlled and sustained delivery of drugs to the targeted sites owing to their unique magnetic particles Size, distribution, and surface change are examples of attributes [3]. The MNP-attached particles can be summarized or coupled on the superficial of a magnetic nanosphere, and they can be given systemically or nearby. They are concentrated in the tumor site by applying an external magnetic field (EMF) [7, 15].

When it comes to distribution to some organs, such as the bone, using an EMF could be problematic. Magnetic implants, in which medications are connected to MNPs to produce a driving force for delivery, appear to be a feasible alternative in these circumstances [13]. These limits can be designed/altered to communicate healing functionality by growing universal flow and biocompatibility, as well as paying inert and lively targeting devices to the tumor site by covering or coupling various physically active therapeutics or minor particle medicines [3].

Chemotherapeutics

Classically, therapy with chemotherapeutic drugs is current incomplete or no targeting volume to exact growth cells, which principal to numerous unwelcome and occasionally plain cross effects. The targeting-based approaches are good strategies to increase the treatment efficiency and to reduce the dose and toxicity of drugs used in the treatment of cancer [10]. A group of chemotherapeutics connected to MNPs, which includes small molecule medications including paclitaxel, 5-fluorouracil, temozolomide (TMZ), and doxorubicin, is a subclass for drug delivery [16].

Here, MNPs are internalized through endocytosis. Furthermore, the internalize process can be facilitated via receptors that are specific. The medicine is released after it reaches the target cells' cytoplasm, and MNPs are usually biodegraded.

MNPs are also frequently functionalized with antibodies in order to boost their ability to penetrate the targeted tumor cells. The antibody-conjugated MNPs could be utilized for more than just targeting; they could also be used to treat, diagnose, and prevent cancer recurrence [16, 19].

Radio therapeutics

The half-lives of the radioactive isotopes to be employed in therapy must be long enough to effectively destroy tumor cells while causing no harm to adjacent healthy tissue. MNPs can be loaded with radioactive isotopes or radionuclides, just like chemotherapeutic-laden MNPs. The radionuclide-loaded MNPs are led to tumor cells and kill them through continuous irradiation after internalization [16].

By decreasing off-target tissue damage, radionuclide-loaded MNPs have distinct advantages over conventional radiotherapy (RT) treatments. Furthermore, ROS produced by radiotherapeutics not only increases tumor death but also improves irradiation response [22].

Gene therapy

Gene therapy holds great promise in the treatment of cancer. Patients with a genetic condition have traditionally been treated using exogenous DNA to fix mutations that cause the disease. The effectiveness of introducing nucleic acids into target cells needs to be enhanced in this method. Furthermore, DNA has a short life span since it degrades quickly in our bodies. Therefore, MNPs may pose a significant role in the augmentation of the gene transport to the specific target tissues [23]. Conjugation of the viruses/plasmids carrying nucleic acids to MNPs protects the viruses/plasmids from inactivation by the immune system and allows them to be transported to specific sites. This process is called attractive transfection or magnetofection gene therapy. Plank *et al.* injected plasmid DNA encoding a cytokine associated with magnetic nanoparticles directly into the tumor and fixed it there by means of a magnet. Thereby, it reduced the probability of recurrence after surgery due to the activated immune system against the tumor [24]. But it is too early for the utilization in clinical therapy and version to non-viral transfection of biomolecules (e. g., DNA, siRNA) due to scarce unexplained issues [16].

Immunotherapeutics

Cancer immunotherapy is the utilization of the body's own immune system to attack cancer cells. It involves several approaches using immune checkpoint inhibitors, monoclonal antibodies, and adoptive cell therapies, and non-specific cancer immunotherapeutics, immunomodulators of tumor microenvironment [25].

Usually, the currently available anticancer immunotherapeutic agents are systemically administered, which leads to low efficacy and high toxicity. Thus, local administration of NP-loaded immunotherapeutic against cancer have gained promising importance [25]. MNPs loaded with cancer immunotherapeutic agents such as cancer antigens, cytokines, and adoptive cell therapeutic moieties could be embattled to the tumor place by request of an EMF [26]. Localizing immunotherapy improve both systemic anticancer immunity and reduce negative effects such as nonspecific immune response, side effects, and inflammatory processes [24].

MNPs as intrinsic anticancer agents

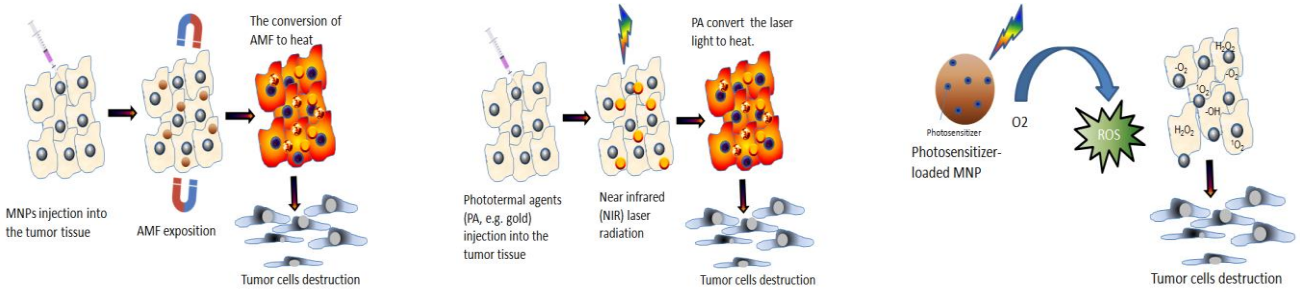
MNPs as an anti-cancer agent

The underlying mechanism of the intrinsic effect of the inorganic nanoparticles themselves on diseases is still unclear. Recently, it was demonstrated that FDA-approved iron oxide NP formulation (ferumoxytol) can kill cancer cells through a ROS-dependent mechanism. In addition, it was proven that it induced a phenotypic shift of macrophages from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype, resulting in the production of ROS, which may induce cancer cell apoptosis [27].

MNPs as a catalyst for tumor ablation therapies

Tumor ablation therapies that use MNPs in tumour therapy have sparked a lot of interest. This type of therapy can be divided into three categories: 1) attractive hyperthermia (MHT) (necrotic

tumour obliteration by warmth made by MNPs when an outside attractive field is practical consecutively); 2) photothermal therapy (PTT) (cancer cell death by heat made by MNPs when well-lit is produced); and 3) photodynamic therapy (PDT) (cancer cell death by cytotoxic undershirt oxygen class made by MNPs conjugate with the photosensitizing agent) (fig. 3).



a. MHT **b. PTT** **c. PDT**

Fig. 3: Schematic representation of three main categories in MNP-based cancer therapy: a. Hyperthermia Therapy (MHT): Following the targeted MNPs delivery to, tumor cells are exposed to an alternating magnetic field (AMF). MNPs locally convert AMF energy into heat, which inducing tumor necrosis. b. Photothermal hyperthermia (PTT): Following the targeted MNPs delivery to tumor cells, photosensitizing nanoparticles (like gold nano shells or similar) the tumor are exposed to near-infrared (NIR) laser radiation. The gold photosensitizing nanoparticles convert the laser light into heat, which inducing tumor necrosis. c. Photodynamic therapy (PDT): Photosensitizing agents attached to MNPs are activated by an external light source to create reactive oxygen species (ROS), which are toxic for cells

All these strategies can individually be used. Even so, the best therapeutic effect is generally assured by a combination of them since their modular design enables MNPs to perform multiple functions simultaneously [10].

Magnetic hyperthermia (MHT)

Cancer treatment using magnetic hyperthermia (MHT) is one of the most effective therapeutic methods. The local temperature is augmented to worth between 42° C and 47° C for at least 30 notes in this application [10]. The forte and incidence of the attractive field, size and attentiveness of MNPs, and answer viscidness are significant limits in the competence of the heat cohort. Using a heat-labile coating, MHT can also help for the distribution of cytotoxic substances to tumorous parts in a controlled way [28].

The intra-tumoral and intravenous administration of the MNPs are the most popular ones among several application routes in this method. In the intra-tumoral route, MNPs are initially inoculated straight into the tumor, trailed by the request of a high-frequency irregular attractive field (AMF). MNPs generate significant local heat by spinning back and forth and cause the destruction of the tumor. The local temperature increase in the tumor site also makes also cancer cells more susceptible to chemo-or radio therapeutics. In this way, it allows combination therapy and greatly reduces the negative side effects of chemotherapy or radiation [18].

Since the MNPs can deliver themselves anywhere in the body via intravenous applications, this might be an appealing therapy option for deep-seated malignancies. In addition, a simple injection into the bloodstream would let MNPs find their own way into cancerous tissue, wherever it is found in the body. Even metastasized cancer would become a target if they sized their particle correctly [29].

Photodynamic therapy (PDT)

PDT is a treatment approaching that uses a drug activated to kill cancer cells, for an external light source is used to excite them. To enhance the effect, these drugs may be conjugated to MNPs. PDT combines a two-stage which consists of a drug (photosensitizer or photosensitizing agent) to damage cells and a particular light to activate the drug. The photosensitizer is either applied via intravenous or locally basing on the body part. The drug is engrossed by the cancer cells and afterward, a sure quantity of time the light is practical to the part to be preserved [3]. PDT has an antitumor activity relying on the generation of ROS; hence, the presence of oxygen is essential [30].

Photothermal therapy (PTT)

PTT is a resident action sense modality used to persuade cancer cell passing with the warmth made in the tumor flesh afterward contact to close infrared (NIR) light. The method is minimally invasive and has minimal toxicity. Incorporating a MNP delivery system, such as gold or carbon coated-MNPs, results in an improvement in the efficiency of heat production in tumor tissue, with excellent safety. This kind of application may lead to a marked increase in NIR absorption compared with magnetic Fe_3O_4 NPs. PTT, unlike PDT, does not require oxygen in order to generate its cytotoxic effect on cancerous cells [32].

Combination therapy

MNPs are used in several different individual ways for cancer therapy. On the other hand, combination therapy is frequently used in order to achieve an enhanced therapeutic effect by synergism. Using EMF enhance the magnetically direction of MNPs-loaded therapeutics (e. g., suicide gene, chemotherapeutics) to the tumor site and AMF causes local hyperthermia in the tumor site. The combination of treatments also results in more reduction in tumor sizes and decreases toxicity [33, 34].

When it comes to multifunctional NPs, trimodal PDT/PTT/CT may be the optimum combination of regimens among numerous options for achieving a synergistic therapeutic effect. In PDT, interactions amid a photosensitizer and oxygen in the flesh crop sensitive oxygen class (ROS), which killing growth cells. Photo-absorbing resources crop warmth in PTT, which kills tumor cells. As a consequence, the cellular preoccupation of attractive nanoparticles is increased in a cooperative way, and the announcement of chemotherapeutical medicines into growth matters is triggered [22].

Joint therapy of attractive hyperthermia with ionizing energy or chemotherapy has strong-minded a cooperative result on an amount of cancers, which subsequent in outstanding tumor reversion. For example, RT combined with MHT made decent consequences on affected role sorrow with glioblastoma and was accepted for scientific hearings years ago. Like this, CT was combined with hyperthermia, which was a very effective treatment of advanced pelvic cancers [21].

Many combination options are possible to achieve a synergistic effect. For example, the radionuclide-loaded MNPs can be combined with the others, such as chemotherapy or gene therapy. Like this, a combination of MNPs-loaded with antibodies and chemotherapeutic drugs is another option. The studies have demonstrated that the combinations have great promising potentials.

Aires *et al.* successfully applied a multi-functionalized iron oxide MNP with anti–CD44 antibody and gemcitabine derivatives for the selective treatment of CD44-positive cancer cells. In addition, Huang *et al.* have achieved very good results with a dual-targeting therapy

involving magnetic Fe_3O_4 NPs grafted with a single-chain antibody and docetaxel loaded β-cyclodextrin in an ovarian cancer [36, 38].

The role of MNPs on cancer drug resistance and metastasis and their role on cancer drug resistance

Surgery is still the gold standard for the treatment of most solid tumors. Although they have limitations, radiotherapy and chemotherapy are other options. Because the tumors are mostly located in hard-to-reach areas for surgical operation and have metastasized. Some types of cancer also have drug and radiation resistance that is pre-existing or developed in the course of treatment. This is frequently the cause of recurrence after CT or RT. The resistance may be against a single drug or simultaneous to several different chemotherapeutic agents (multidrug resistance) thorough various mechanisms [16].

MNPs allow for the functionalization of one or more active chemicals and the combination of substances with a wide range of modes of action. As a result, they have the ability to use multiple therapeutic mechanisms at the same time, considerably reducing the risk of resistance. For example, a triple effect can be achieved with a combination of hyperthermia, CT and RT using MNPs with a magnetic core (such as zinc, iron oxide), chemotherapeutic agent (such as folic acid, cisplatin) and the radioactive material (like 188 rhenium) [38].

Ideally, the functionalized and biocompatible coated MNPs should have components to meet different tasks, including antitumor effects, overcoming cancer drug resistance, diagnostic/imaging investigations and enhancement at the target site [16].

Metastasized cancer–limitations and possibilities

Approximately 50% of tumors have already spread at the time of diagnosis. Therefore, most of these patients can only be offered palliative care. However, there are approaches with therapeutic purposes targeting metastatic cancer. For example, the magnetic hyperthermia transduced by super paramagnetic iron oxide nanoparticles (SPION) in the alternating current magnetic field may be used to reduce or eliminate cancer stem cells (CSC) population. Because CSCs not only can play a major role in cancer initiation, progression and drug resistance but also these cells survive and migrate to distant sites. The combination therapy monoclonal antibody/chemotherapeutic or radioactive substance loaded SPION will led to the significant reduction of tumor growth [16, 38].

Removal of circulating cancer cells

Stem cell transplantation (SCT) is a procedure to restore healthy bone marrow in patients with leukemia. Before SCT, the patient receives high doses of chemo-, and sometimes radiotherapy, which kill not only neoplastic cells but also healthy cells. In addition, multidrug-resistant mechanisms to conventional chemotherapeutics ensure dormant cells, considered as cancer stem cells, cause recurrence of the disease [39].

Functionalized MNPs has become an area of interest that can provide extracorporeal removal of unwanted cellular entities from the blood. However, there are several challenges for the functionalization of MNPs with a suitable targeting agent, such as a peptide or an antibody, to bind the specific target [40].

In our opinion, an alternative approach is to support the recirculation of healthy cells of the patients after the separation of cancerous cells targeted by MNPs-loaded with specific molecules. An appropriate extracorporeal device system is required for this application, which provides for effective injection, mixing, and removal of MNPs in order to separate the targeted malignant cells. CTCs are the key factors in the metastatic process and for the poor outcome of cancers. Hence another alternative could be the removal of the CTCs from blood circulation using functionalized MNPs.

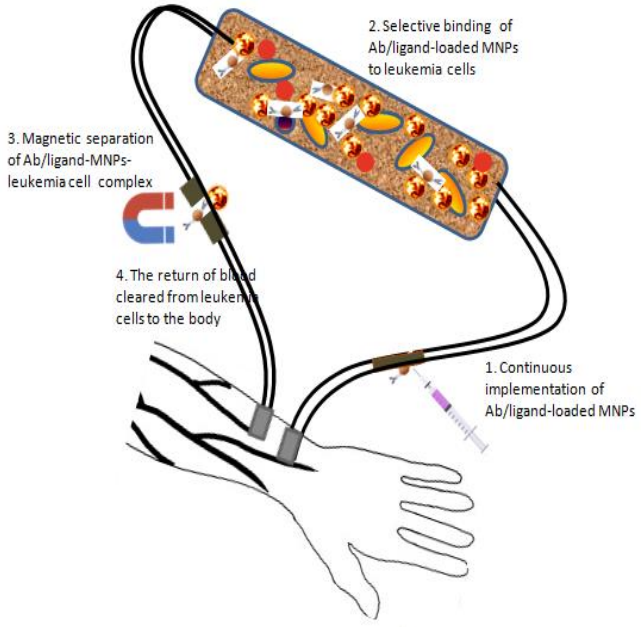


Fig. 4: Schematic demonstration of the process of leukemia cells removal from the blood using MNPs carrying ligands/antibodies targeting leukemia cell-specific/over expressed antigen

CONCLUSION

The use of MNPs for effective cancer therapy has made significant progress. MNPs enable the transport and delivery of a wide range of substances (chemotherapeutics, radionuclides, antibodies, immunomodulators, viral vectors carrying genes, and so on) to the target location where they are intended to work. Besides, it is possible to achieve synergistic effects in order to improve the desired anticancer effects by combining two or more of them. The combination to aim diagnostic and therapeutic (Theranostics) goals in cancer treatment is certainly another important aspect in the use of MNPs. Other side, there is much more things to be discovered relevant to the use of MNPs for cancer therapy. Despite the successful studies, their clinical applications seem remote to be used in complete safety due to some unpredictable barriers such as excretion and long-term toxicity. MNPs are promising prospects with a wide range of biomedical applications, including cancer detection, therapy, and monitoring.

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AUTHORS CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICT OF INTERESTS

All authors declare that there is no conflict of interest.

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