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The role of nanomedicine in the treatment of osteosarcoma and in the prevention of infections

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Abstract: Osteosarcoma is the most common bone cancer in children and the third most common cancer in adolescence. The current survival rate for osteosarcoma is 60-70% which has not improved over the past two decades. The treatment of osteosarcoma is complicated by cytotoxicity and side effects of various therapeutic drugs and osteosarcoma can also be accompanied with infection which can happen post-surgical resection or can be associated with implants causing graft rejection. The goal of utilizing nano-medicine in the treatment of osteosarcoma is to take advantage of nanocarriers for specific targeted drug delivery to cancer cells and to lower the negative impact of drugs on normal cells. Further, nanoparticles can prevent infections in patients. In this paper, we review specific nanomaterials, various micelleplexes, and their role in targeted drug delivery to osteosarcoma cells. We will also review the anti-cancer effect of nanoparticles that should replace chemotherapy in the future. This paper also reviews the role of nanoparticles in passive and active targeting of osteosarcoma cells and the role of nanocomposites in cancer treatment and infection prevention in the osteosarcoma.

Keywords: *Nanomedicine, Nanoparticles, Osteosarcoma, Nanocarriers, Micelleplexes, Active Targeting, Passive Targeting*

OSTEOSARCOMA: A DEBILITATING CANCER PREVALENT IN CHILDREN

Osteosarcoma (OS) is the most malignant bone cancer in which immature bone cells (in osteoids) are produced by tumor cells. Although OS is a rare bone tumor with a global incidence of only 3.4 cases per million people per year, it is the most common bone cancer in children and the third most common cancer in adolescence. From the 1000 new cases of osteosarcoma diagnosed each year in the United States[25], 450 occur in children. OS is the most common in the second decade of one's life. Further, the current survival rate for OS is about 65%. [8] [25] 70% of cases show chromosomal abnormalities and a few cases have cell cycle regulation defects. Mutations in tumor-suppressor genes and DNA helicases show abnormalities in OS. tumor samples.[14] What makes OS even more detrimental is that it is often a secondary cancer type where cancer from other parts of the body often metastasize to bone, making treatment and recovery even more complicated.

CURRENT OS DIAGNOSIS

For every bone lesion, the imaging protocol to determine if OS exists starts with X-ray analysis and is followed up by MRI imaging and CT scans. The X-ray protocol includes at least 2 angles and each X-ray must show two adjacent joints on two sides of the lesion. OS on an X-ray image appears as an ill-defined lesion usually in the long bones, arising from the metaphysis of bone, including osteoblastic and osteolytic areas, with a periosteal reaction and soft tissue mass[23]

MRI imaging is used to evaluate the soft tissue mass, the extension of the tumor and possibly bone marrow invasions along with neurovascular structures. CT scans can reveal cortical invasion, fracture sites and the extent of involvement and metastasis [23]. The final diagnosis of OS is through a biopsy.

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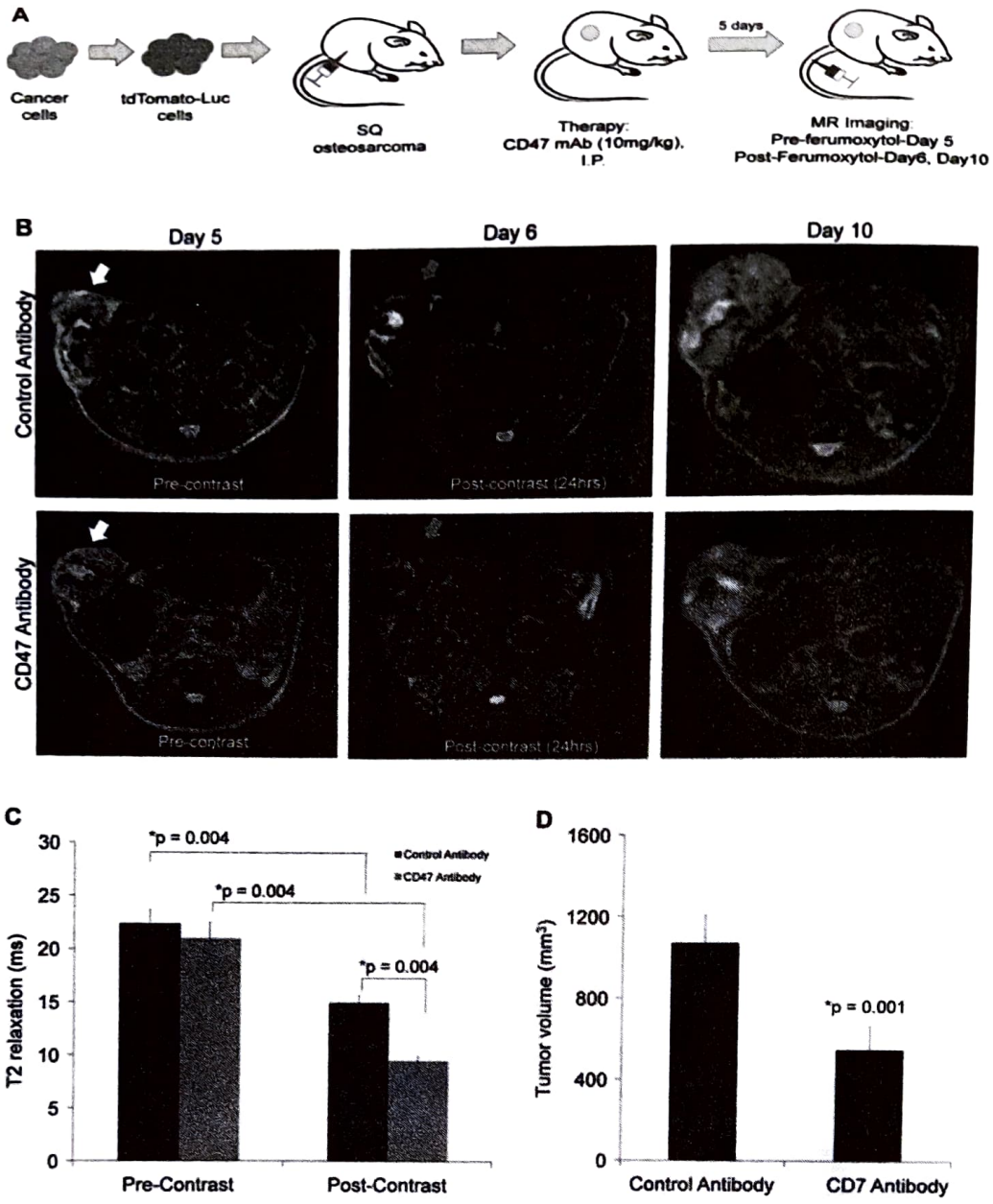

Fig 1. ***Ferumoxytol-enhanced MRI images by Mohanty et al demonstrating the promise of nanomaterials to improve osteosarcoma diagnosis, Credited to Mohanty, et.al. 2019*** [25]

Nanoparticles have provided new aspects for the usability for MRI imaging in research and visualization of the macrophage response to immunotherapy in osteosarcoma. CD47 monoclonal antibodies (mAbs) induce an immunological response by activating tumor-associated macrophages (TAMs) through which TAMs will be able to remove osteosarcoma cells through phagocytosis. These immunological responses to CD47 antibodies have to be monitored with specific diagnostic tests to prove the efficiency of CD47 mAbs. For example, Mohanty et al. used Ferumoxytol, a nanoparticle, as a contrast agent that could be phagocytosed by TAMs and be detected by MRI (Figure 1). Ferumoxytol-enhanced MRI successfully detected TAM responses to CD47 mAbs in mouse models of OS and was suggested to be used in clinical trials to monitor CD47 mAbs treatment [26, 27].

A. The study started vis for Figure 1 subcutaneous injection of human osteosarcoma tumor cells to mouse models. After the detection of tumors with bioluminescent imaging, control antibodies and anti-CD47

mAbs were given to the control and case groups, respectively. Ferumoxytol-enhanced MRI was performed on days 5, 6 and 10.

B. T2-Weighted MRI images of osteosarcoma in mice treated with the control or CD47 mAbs. The tumor is bright (hyperintense) in pre-contrast MRI images whereas after administration of ferumoxytol, the tumors seem hypo-intense enhancement (dark, red arrows).

C. Tumor MRI enhancement is measured by T2 relaxation time. The T2 relaxation time is significantly shorter in CD47-treated tumors on ferumoxytol-enhanced images, showing that the ferumoxytol enhanced MRI is more efficient in detecting the tumor response to CD47 antibodies.

D. Tumor sizes on day 10, as represented by ferumoxytol-enhanced MRI scans, were significantly lower in the group treated with CD47 mAbs compared to the control group [26].

Photo credited to Mohanty et al., 2019 [26].

CURRENT OS TREATMENT

The American Cancer Society recommends OS treatment based on its extent of growth in the body. There are several factors involved in choosing the best treatment method for OS including extent of growth, grade, location, the person's age, overall health and accompanying conditions.

The extent of OS is referred to as its 'spread' which is determined through staging the cancer. Staging is done physically through exams, imaging, lab tests and biopsies. The goal is to determine how much cancer is in the body, how far it has spread and what organs are involved.

The simplest level of staging is by categorizing OS into localized and metastatic as described below:

Localized OS. OS is considered localized if it is limited to the bone from which it started based on radiology images and biopsies, with the possibility of extension to the tissues immediately adjacent to the bone such as muscles, tendons and fat tissues. Most of the cases of OS sarcoma start as a localized cancer. However, since in every patient, there is a possibility of long distance metastases that are not visible in imaging studies and are not immediately detectable through lab tests, conventional chemotherapy is a main part of the treatment.

Surgical Treatment for Localized OS. Surgical treatment for localized OS depends on whether the cancer is resectable or non-resectable. If the entire visible tumor can be removed by surgery, it is a resectable tumor. Non-resectable tumors are the ones that cannot be completely removed by surgery.

Metastatic OS. When OS spreads to other parts of the body, the treatment and prognosis will be more challenging. The most common sites for OS metastasis are other bones, lungs and the brain. Unfortunately, 1/5 of all OS have long distance metastasis at the time of diagnosis.

STAGING AND GRADING OF OS

OS stage can be determined by a physical exam, imaging and biopsies. It is a systematic system to classify the cancer based on how far it has spread. Based on the Musculoskeletal Tumor Society (MSTS) staging system, also known as the Enneking system, 3 factors are used to determine the stage of osteosarcoma:

1 The Grade (G) of the tumor: Tumor grade is determined under the microscope. Tumor cells can be classified as low-grade and high-grade. Low-grade tumor cells are closer in appearance to normal cells and usually have a lower chance to metastasize quickly. High-grade tumor cells are more abnormal and represent a tumor that can spread fast.

2 The extent of the primary tumor (T): Classified as intracompartmental or extracompartmental. Intracompartmental tumors remain in the organ or structure where they formed, while extra compartmental tumors are the ones that extend to nearby structures.

3 Metastases (M): Meaning whether the tumor has spread or is nearby or farther away from organs. Tumors with no metastases to any nearby or farther away organs or lymph nodes, are considered M0, whereas tumors that have spread locally or over a long distance, are classified as M1.

The staging of a tumors uses Roman numerics. Stages I and II are divided into A (intracompartmental tumor) and B (extracompartmental tumors) (American Cancer Society, 2020) (Table 1).

Table 1.

Stage	Grade	Tumor	Metastasis
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	G1 or G2	T1 or T2	M1

Osteosarcoma Staging.

Credited to the American Cancer Society.

Chemotherapy Regimens for OS

Despite the existence of some low-grade variants, most OSs are highly malignant. There are multi-modal treatment regimens for high grade OS, and specifically, preoperative chemotherapy has improved the prognosis and achieved a long-term survival in 2/3 of the patients [3]. Prior to the introduction of chemotherapy in the 1970s, the treatment for OS was limited to surgical resection which led to a <20% cure rate in patients. The leading cause of mortality in patients who underwent surgical resection without chemotherapy was lung metastasis. After the introduction of chemotherapy, the use of a combination of surgery and chemotherapy has led the 5-year survival rate to reach 70%. This rate of survival has not improved over the past two decades and the majority of survivals are among pediatric patients. The prognosis for adults remains poor [29].

The chemotherapy regimen for high-grade OS usually has a duration of 6-12 months. Doxorubicin is a main chemotherapeutic component of this treatment regimen along with Cisplatin and high-dose Methotrexate. The major concerns with the current chemotherapy regimen (despite its achievements in improving the prognosis and increasing the survival rate from 20% before 1970s to 70% mostly in pediatric patients today[29]) is the toxicity associated with each of the mentioned drugs. Doxorubicin's use must be limited and closely monitored because of its cardiotoxicity while Cisplatin has shown some renal toxicity and high doses of Methotrexate has the potential of life-threatening toxicity but it is usually tolerated by younger patients. [3] Other complications of chemotherapy include the suppression of bone marrow cell growth, inflammation of mucosal surfaces, impaired renal function, cardiotoxicity and hypomagnesemia which can lead to arrhythmia, hearing loss, gonadal dysfunction and ultimately, infertility.[3] In approximately 1/3 of patients who have a complete positive response to treatment, a relapse can occur. For example, in a study that followed up on 37 patients with localized OS of the extremities and relapsed, unfortunately, 31 patients died (29 within 6 years of the recurrence and 2 more than 6 years from the recurrence). 6 of the 37 patients with an OS relapse lived between 6-24 years from the first recurrence and 5 of them lived disease free for this period of time and 1 with the disease. [7] Therefore, for OS, metastasis and

recurrence of a bone tumor at the site of resection are two major challenges in the treatment of OS and in the patient's prognosis.

On the other hand, the plateau of a 60%-70% rate of a 5-year survival in OS for the past 2 decades is related to chemotherapy drug resistance [21]. The relatively high chance of distant metastases and a lack of improvement in the survival rate since the 1980s, point to a strong need for new technologies for drug delivery and this need is undeniable.

Another serious concern in the treatment of OS is postoperative infection and how it can affect the survival in OS patients. In general, post-treatment complications in OS include infection, local recurrence, wound infection, pathological fractures, and prosthetic loosening. The incidence of infection in OS patients is 5.3-13% making it a major complication. These infections can have a range of severity from mild to very severe and deep infections are the cause of readmission, revision surgeries and amputations. According to the association of postoperative infection and improved survival in osteosarcoma patients, although postoperative infections in osteosarcoma patients can be associated in prolonged survival, the quality of life and outcomes remain controversial [6].

THE DEFINITION OF NANOTECHNOLOGY IN MEDICINE AND ITS ROLE IN IMPROVING THE SURVIVAL RATE AND QUALITY OF LIFE

Nanotechnology involves the application of particles in the nanoscale regime (1-100 nanometers) to create new solutions for all different scientific fields including medicine, chemistry, physics, agriculture and different areas of engineering [28].

Nanomedicine or the implication of nanotechnology in medicine is a progressive field with high potential in research and medical technology and treatment as nano-materials and nano-devices have been well studied in vitro and in vivo. Nanoparticles can be used for targeted drug delivery, especially where drug delivery is challenging such as across the blood brain barrier or across the placenta. Nanoparticles can be used as drug carriers not only to transfer drugs across more specific biological barriers but to protect healthy cells from the side effects of drugs by improving bio-distribution of drugs. Nanotechnology can also be used in the regenerative medicine and in manufacturing implants resistant to infections [2].

Nanotechnology may be that answer to what has complicated the treatment and the survival rate of OS. Nanotechnology has provided the possibility of loading high doses of drugs and other molecules into nanocarriers that are capable of targeting specific receptors on cells and even entering the cells to release its drug payload. These methods, by specific targeting and by lowering the required dose of the drugs can increase drug efficiency and reduce side effects [3].

Most importantly, the successful delivery of chemotherapy drugs and RNAi are challenges that can be addressed by utilizing micelleplexes. Micelleplexes are complexes of cationic amphiphilic blocks copolymers with a micelle-formed configuration. Genetic materials such as nucleic acids (NAs) including plasmidic DNA (pDNA), small interfering RNA (siRNA) and micro RNA (miRNA) can be loaded into micelleplexes as the nanocarrier to deliver NAs to osteosarcoma cells [3]. Micelleplexes are attracting attention as successful nano-platforms for the effective and targeted delivery of NAs and chemotherapy drugs [3], [1].

Several nanoparticles have been used to optimize the treatment of OS (Table 2), including but not limited to:

1 - Alendronate-modified polydomaine-coated paclitaxel nanoparticles:

Paclitaxel (PTX) is an approved medicine for several types of cancer, however, there is not enough evidence to prove its efficacy for the treatment of OS. Nevertheless, PTX was used by Leo and his team as a model drug

for the targeted treatment of OS cells in vitro. The efficacy of PTX is limited by its low bioavailability and high toxicity and low water solubility. However, in the above mentioned study, nanocarriers were created for PTX. These nanocarriers were made by synthesizing new nanoparticles that were coated with polydopamine (PDA) and then alendronate (ALN) was grafted to them as a ligand with an affinity for OS cells. The conjugation of PDA-NPs with ALN ligands created nanocarriers for PTX. These nanoparticles showed higher in vitro affinity and cytotoxicity for K7M2 OS cells. They also showed lower side effects and a higher therapeutic efficacy than PTX alone (82.51% vs 66.63%). The authors concluded that PTX-PDA-ALN-NPs could be a potential drug for the treatment of OS [20].

2 - Gold nanoparticles:

Gold nanoparticles (AuNPs) have shown size-dependent cytotoxicity on OS cells. The cytotoxicity and uptake of gold nanoparticles can vary based on their size. In a study focused on gold nanoparticles of 40-60 nm, increasing the concentration of the 46 nm AuNPs enhanced apoptosis in MG63 cells. This enhancement in apoptosis was achieved by the disruption of mitochondrial membrane potential. Higher cancer cell death rate was observed for the 46 and 60 nm AuNPs compared to 38 nm at 200, 400 and 800 ng/ml concentrations. Cellular apoptosis was assessed by surface enhanced Raman scattering (SERS) [4].

3 - Tangeretin-assisted platinum nanoparticles:

Doxorubicin (DOX) is a common chemotherapeutic drug for the treatment of OS. Its severe side effects though, still limits its use. The anticancer activity of a combination of platinum nanoparticles (PtNPS) and DOX on human OS epithelial cells (U_2OS) was investigated. The combination of PtNPS characterized by tangeritin and DOX significantly lowered U_2OS viability and proliferation in a dose-dependent manner. This combination also increased lactate dehydrogenase leakage, reactive oxygen species (ROS) generation, and caused mitochondrial dysfunction detectable by a reduced mitochondrial membrane potential (MMP)[12].

4 - Hydroxyapatite nanoparticles:

Hydroxyapatite nanoparticles (nano-HAPs) synthesized by Wang and colleagues, reduced the viability of OS-732 cells in mouse tumor models and decreased the migration and invasion of normal cells in vivo. The down regulation of OS-732 cells by nano-HAPs was achieved by slowing the FAK/PI3K/Akt signaling pathway (a signaling pathway activated by the platelet-derived growth factor). This study showed the efficacy of nanoHAPs in suppressing OS-732 cells in vitro and in vivo [40].

Table 2

NPs	Role	Effect	Reference
PTX-PDA-ALN-NPs	Nanocarrier for PXT	Lower side effects and higher efficacy than PTX alone (82.51% vs 66.63%).	[36]
AuNPs	Anti-cancer nanoparticles	Size-dependent cytotoxicity on OS cells.	[37]
PtNPS	Nanocarrier for DOX	Reduced U_2OS viability & mitochondrial dysfunction in MG63 cells.	[38]
nano-HAPs	Anti-cancer nanoparticles	Reduced OS-732 cells viability, migration and invasion.	[39]
ANPs	Drug delivery system for DOX	Cytotoxicity close to DOX alone with fewer side effects.	[40]

5 - Aragonite nanoparticles:

Another drug delivery system utilizing nanotechnology has used cockle shell-derived aragonite nanoparticles (ANPs) and loaded them with doxorubicin (DOX). DOX-ANPs showed a faster DOX release at a pH of 4.8 compared to pH of 7.4. Flow cytometric analysis showed cell cycle arrest in OS cells induced by DOX-ANPs. The cytotoxicity of DOX-ANPs was close to the cytotoxicity efficacy of DOX alone. The researchers concluded that DOX-ANPs could act as a pH-sensitive drug delivery system for the treatment of OS. This study was conducted in vitro [9].

Passive Targeting OS Nano Therapies

Targeted drug delivery is the process of drugs being selectively delivered to targeted cells. Passive targeting uses cellular mechanisms to uptake the drug, such as endocytosis instead of actively transferring the drug into the cells.

Passive targeting uses lipid-based nanoparticles, such as liposomes, polymeric micelles, and gold nanorods to name a few (Table 3), which will be described next.

Liposomes: Liposomes are particularly useful for the delivery of Doxorubicin. Liposomal Doxorubicin is formed when Doxorubicin is encapsulated in a liposome. In this vesicular structure, Doxorubicin is inside a lipid hydrophobic shell that is coated with PEG for stability. These liposomes can be ingested easily by OS cells and overall, improve drug delivery, and elimination of OS cells [1].

Table 3

Nanocarrier	Composition	Findings
ZnO Nanoparticles	Zinc oxide nanoparticles	Induce autophagy and apoptosis in OS cells [15].
PLGA Nanoparticles	Polylactic co-glycolic acid + PEGylated Polylactic co-glycolic acid	Controlled release profile and enhanced cell cycle inhibition activities [39].
Dextran-based Nanoparticles	Lipid modified dextran	Delivery of siRNA to OS cells [43].
Lipid-coated Polymeric Nanoparticles	Lipid-coated polymers	By delivery of microRNA, they inhibit the growth and proliferation of OS cells [43].
Hydroxyapatite Nanoparticles	Hydroxyapatite coating, polyvinyl alcohol conjugated methotrexate	Supporting proliferation to normal bone cells and inducing apoptosis in OS cells [43].

Passive Targeting Strategies in OS treatment

Polymeric Micelles: Polymeric micelles are colloidal suspensions that can be used both in cancer diagnosis and treatment. Micelles are used as nano sized cylindrical, spherical, or ellipsoid structures composed of hydrophobic and hydrophilic components. Recently, hybrid nanomicelles have been formed by integration with metal nanoparticles such a gold, iron-oxide, and silver. Gold nanoparticles in the size range of 40-60 nm have shown noticeable cytotoxicity on OS cells at 200,400, and 800 ng/ml concentrations [4]. According to recent studies, the interaction between immune cells (macrophages) and iron oxide nanoparticles can lead to anti-tumor immune responses. This effect is in addition to the efficacy of iron oxide nanoparticles in treating anemia in patients suffering from different types of cancer, including OS [35]. 5 nm and 35 nm citrate-coated silver nanoparticles (AgNPs) can induce death in OS cells (U_2OS and Saos-2 Cells) regardless of their p53 status. Therefore, AgNPs are attractive novel candidates for chemotherapeutic treatments of OS [19]. Polymeric micelles can deliver water insoluble or poorly water soluble drugs, lengthen their stability, and enhance their potency (therapeutic efficiency) through site-specificity and increased anti-cancer drug penetration [13].

Gold Nanorods: Polyacrylic acid-coated gold nanorods have been used in photo thermal therapy to treat OS. In a study by Pan et. al., it was demonstrated that polyacrylic acid (PAA) - coated gold nanorods (GNRs) when stimulated with a 808 nm laser, increased the efficiency of hyperthermia therapy for MG63 human osteosarcoma cells. It was shown that GNRs-PAA can increase the efficiency of photo thermal therapy by damaging cell membranes causing DNA integration that leads to apoptosis in OS cells. This experiment was conducted in vitro by planting MG63 cells into 96-well plates with H-DMEM medium and the effect was proven to be dose-dependent [31].

Active Targeting

Multiple nanoparticles have been used for active targeting to OS cells. The mechanism of active targeting is bonding molecules (such as ligands and antibodies) to the surface of nano-carriers, some of the same ones mentioned above for passive targeting. Therefore, they enhance cellular uptake of drugs by targeting compatible cell receptors and cell membrane channels. These mechanisms take advantage of the over-expression of receptors on the surface of cancer cells. These receptors include folate receptors that are over-expressed in OS xenograft samples, $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins, type-A receptor 2 (EphA2), a surface molecule over expressed in OS cells, CD133, epidermal growth factor receptor (EGFR) and CD44 [41].

Ligand-targeted drug delivery nano systems currently rely mostly on folic acid receptors and transferring receptors [18]. Although folate α receptors are over-expressed on the surface of OS cells, there are also folate uptake mechanisms inside OS cells that can increase cellular resistance to chemotherapy. In order to overcome multi-drug resistance in cancer cells, the co-delivery of drugs and nucleic acids (NA) is considered a method to increase the intracellular concentration of chemotherapy drugs and/or activating apoptotic pathways. Micelleplexes are nanostructures used to achieve this goal showing much promise and will be described next.

Micelleplexes

Multifunctional nanostructures that deliver genetic material and chemotherapy to OS cells are promising [32]. Micelleplexes are nanocarriers formed from polymer-based nanosystems. Since RNA interference (RNAi) technology has started a new approach in treating cancer through the use of nucleotide interfering molecules to inhibit different phases of cancer, micelleplexes are valuable in cancer treatment and specifically in OS as a nanocarrier for nucleic acids and for chemotherapy delivery [32]. This method is fairly new. In a study in 2018, researchers decided to use a nanosystem to deliver genetic material to repress the expression of mutated genes in the regulatory pathway of OS. An efficient micellar nanosystem was developed by conjugating the amphiphilic copolymer Pluronic® L64 and the cationic polymer polyethileneimine (PEI). This combination was used to deliver miRNA-145 into the OS cells which resulted into the arrest of proliferation and migration and ultimately induced apoptosis in OS cells [22].

Polymers

Polymers, such as Methotrexate conjugated with poly glycerol adipate, can self-assemble into nanoparticles. The size of the nanoparticles depend on the dose of the conjugates, MTX and the pH of the medium. The MTX-PGA conjugates containing high molar MTX content (27.5 mole) showed a higher toxicity for Saos-2 cells compared to free MTX. These nano particles were physically stable at a pH of 5-9 and chemically stable at a pH of 7.4 against hydrolysis for 30 days. However, they can be degraded by enzymes to release MTX [37].

Suppressive Treatment

Suppressive therapy in cancer is a course or multiple courses of treatment to prevent the growth of any remaining cancer cells [10]. Magnetic gene carriers made of polyethylenimine, dextran and iron oxide nanoparticles (PDIs) have been used for the in vitro and in vivo transfection of miR-302b [8]. miR-302b belongs to a group of short non-coding RNAs or microRNAs (miRNAs). MiRNAs have a rssss der-expressed in OS cell lines while it is expressed more predominantly, in healthy osteoblasts cell lines. miR-302b can in fact, limit the proliferation of OS cells and induce apoptosis in these cells [42]. PDIs have shown mild toxicity in mice. By the use of a magnetic field, PDI/pmiR302b entering the OS cells of mice showed effective anti-cancer effects with low toxicity [11].

Curcumin-loaded Self-assembled Arginine-rich-RGD Nanospheres

Curcumin shows anticancer affects through different mechanisms. However, its low water solubility is a challenge for using curcumin in vivo.

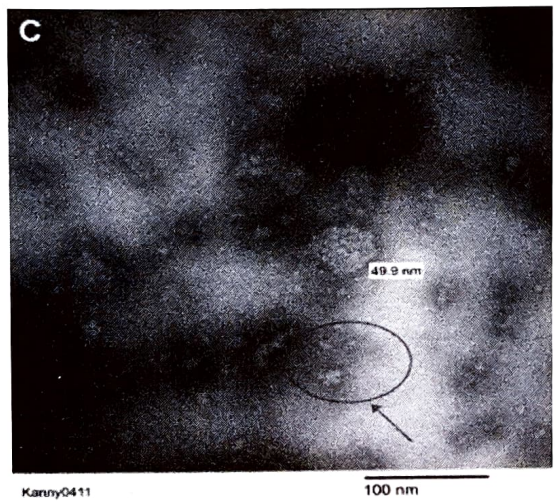

Fig. 2: ***Aggregates of amphiphilic nanoparticles without sonication. Photo credited to Chang et al., 2015[5].***

Therefore, an amphiphilic peptide C18GR7RGDS was recently used as a carrier for curcumin in water-based solutions. The combination of amphiphilic nanoparticles and curcumin APNP/curcumin showed significant toxicity against MG-63 OS cells compared to control cells (normal osteoblasts) (Fig. 2) [5].

Selenium Nanocomposites

The recurrence of OS at the site of tumor resection is a major challenge for a patient's survival and quality of life. An in vitro study, using selenium nanoparticles (SeNP), lowered the recurrence of OS cells and enhanced the function of healthy osteoblasts. SeNPs for this study were formed on poly-L lactic acid (PLLA). Selenium coated PLLA showed increased osteoblast activity (increased ALP) compared to osteoblasts on control tissue culture plates without the use of any chemotherapy or other medicine. These results suggest that selenium coated PLLA should be further examined as a potential graft material to replace cancerous bone tissue [36].

Magnetic ZnF_2O_4-hydroxyapatite nanocomposite particles

Infections are a well-known complication of OS, post-surgical resection and they are also associated with bone implants and are a major reason for amputation and graft rejection. Multifunctional ZnF_2O_4-hydroxyapatite nanocomposite particles were formed through the co-precipitation method. At the concentration of 0.078mg/L, ZnF_2O_4HAp had the highest inhibitory effect on bacterial proliferation and growth on gram positive bacteria.

These nanoparticles could penetrate bacterial cells through endocytosis. Iron-oxide nanoparticles can penetrate bacterial cells due to the fact that their size is smaller than the membrane pores. These nanoparticles can then inhibit the DNA and protein synthesis inside the bacterial cells. Additionally, when zoledronic acid (ZA) was loaded into ZnF_2O_4HAp as nanocarriers, for primary ZA concentrations of 0.01, 0.02, and 0.04 mg/L, the drug-loaded nanocomposite particles showed an early burst release through the first 20h followed by a slow drug release until 170h. Based on these experiments, ZnF_2O_4HAp are multifunctional nanocomposite particles that can inhibit bacterial growth at the site of osteosarcoma and can also be used as localized anticancer drug delivery systems [34].

Conclusion and Future Directions

To increase life expectancy and the quality of life in patients with OS, more specific and targeted therapeutic methods are required. In this article, we reviewed current passive and active targeting OS therapies through nanoparticles. Although there are several benefits to using nanoparticles for drug delivery and increasing the potency and bioavailability of chemotherapeutic medicines for OS, there are concerns about the potential side effects that mandate further and deeper in vitro and in vivo studies. Of note, Micelleplexes have showed significant capabilities in drug and NA delivery into OS cells, however, there are serious concerns about their cytotoxicity [30].

Hydroxyapatite nanoparticles on the other hand, can be a major breakthrough in the treatment of OS through the dual role they play in enhancing healthy bone cells while killing OS cells. They increase the proliferation in normal bone cells while inducing apoptosis in OS cells. These nanoparticles should be the focus of improved OS treatment in future nano medicine studies; although, several more studies are required to assure the absence of cytotoxicity.

From among the active targeting therapies, selenium nanoparticles have shown an effect very similar to HANPs. They also increase the proliferation in healthy osteoblasts and have an inhibitory effect on OS cells.

The use of nanocomposties can revolutionize cancer treatment in osteosarcoma since these particles can have a dual effect of anticancer treatment and infection inhibition. Considering that infection is a major factor that impacts the quality of life and also causes complications in the treatment of OS, nano medicine with the use of nanoparticles, nanocarriers and nanocomposites has the potential to revolutionize the treatment of OS in the future.

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