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Advances in Nanotechnology for Diagnosis, Treatment, and Recovery of Bone Cancer

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Abstract

Introduction: Although effective treatments for bone cancer currently exist, nanotechnology promises to improve the diagnosis, treatment, and recovery from this disease. This paper explores the various ways in which nanotechnology is being explored in relation to the imaging of tumours, the delivery of treatments, and the rebuilding of bones.

Methods: Using computer aided searches, studies from across the globe that highlighted the development of nanotechnology for application in treating bone cancers were located. A total of ten articles were selected for inclusion in this paper because they represent a broad array of nanotechnology applications related to primary and secondary bone cancer.

Results: The results of this research indicate that nanotechnology can be used to detect cancer by identifying tumour biomarkers by amplifying Raman signals, transmitting light wave signals, and by attaching fluorescent nanomaterials. Other studies found that nanomaterials can cause apoptosis of cancer cells while promoting healing in other non-cancerous cells. It has also been found that nanomaterials can deliver mRNA and small interfering RNA treatment directly to the tumour site. Nanomaterials have also been found to be useful as photothermal agents. Not only can nanomaterials be used to stimulate bone regeneration, researchers have also found that it can also be used to create scaffolds which mimic the extracellular matrix of natural bone.

Discussion: Although nanotechnology holds great promise, it also presents several potential dangers. Researchers have found that nanoparticles can be inhaled and may do damage to the lungs. In addition, some researchers note that the introduction of nanomaterials may cause an increase in radical oxygen species which can also harm humans and other species. Therefore, more research is needed to find ways to lessen the impact of these potential harmful aspects of nanomaterials.

Conclusion: Nanotechnology is a relatively new field that has the potential to improve the ways to diagnose and treat bone cancers. However, it is imperative to continue to research the more harmful aspects of nanotechnology so steps may be taken to reduce the risk while increasing the benefits.

Keywords: bone; cancer; nanotechnology; diagnosis; treatment; recovery

Introduction

Due to the aggressive nature of bone cancer and the limitations of traditional treatments which include chemotherapy, surgery, and radiation therapy [1], bone cancer remains a challenge in medicine. When bone cancer originates in the bone, it is known as primary bone cancer while cancer that originates in another part of the body and spreads to the bone is known as secondary bone cancer [2]. The current treatments are effective at treating the cancer but neglect the issue of regenerating the damaged bone. Moreover, traditional bone cancer treatments may lead to an increased chance of tumor reformation due to residual cancer cells or they may cause serious side effects [1]. A new, less-invasive approach using nanotechnology has emerged allowing for the elimination of cancer cells while also promoting post-treatment recovery. Nanotechnology involves nano-materials ranging in size from 1 to 100 nm in a variety of applications [3]. Nanomaterials can be made from various mediums such as gold and carbon, depending on the nature of the application [4].

Nanotechnology can enhance early diagnosis of bone cancers by using nanoparticles as imaging markers in conjunction with imaging techniques such as computed tomography (CT) scans and fluorescence imaging [5]. Major advancements in the treatment of bone cancers have been made using nanomaterials in conjunction with 3-D printing which allows for creating physical objects layer-by-layer based on geometric designs generated on the computer to create customized implants to allow for bone regeneration [6]. Some components created using 3-D printers and nanomaterials have been able to morphologically mimic the extracellular matrix [7]. Nanoparticles have also been used to deliver drugs to promote bone growth to designated parts

of the body with damaged bone, allowing for more effective treatment plans [8].

This paper explores the way nanotechnology impacts diagnosis, treatment, and post-treatment recovery for bone cancer using research from PubMed, ScienceDirect, and OpenMD. The limitations of using nanotechnology in relation to bone cancer were analyzed based on the stated limitations of each study. Suggestions for possible future research are discussed regarding the medical applications of nanotechnology. Therefore, this research will be potentially helpful for identifying gaps in knowledge or future areas of research in the field of nanotechnology.

Methods

Peer-reviewed articles on the impact of nanotechnology in medicine were read and the impact of nanotechnology on bone cancer was specifically noted. Keywords were entered into PubMed, OpenMD, and ScienceDirect to identify relevant literature. In addition, the Boolean operators, 'AND' and 'OR' were used to conduct advanced searches to enhance precision as well as receive more refined results.

Studies on using nanotechnology to help with diagnosing early stages of cancer were found by conducting an advanced search using "(((nano) AND bone cancer) AND diagnosis) OR diagnose." Research conducted about nanomaterials and 3-D printing were collected by completing advanced searches in search engines using the key words "((Nanomaterials/nanoparticles) AND (3-D printing) AND (bone cancer))." The key words "((3-D printing) AND (bone cancer) AND (manufacture))" were typed in later. Research regarding bone regeneration was found by typing in "((nanotechnology) AND (bone healing))" and "((bone regeneration) AND (osteogenesis) AND (nano) AND (cancer))." The way drugs were delivered using nanotechnology was investigated by conducting an advanced search using "((nano) AND (bone-targeted) AND (drug delivery))" as well as "((3-D printing) AND (nano) AND (drug delivery))." Information about limitations regarding the impact of nanotechnology on bone cancer was gathered using the key words "((toxic) AND (nano) AND (bone health))." The experimental design and key findings were noted for each piece of literature. Literature pertaining to recovering from, diagnosing, and treating primary as well as secondary bone cancer was analyzed in this review. Not every study pertaining to this topic was included. Since many were replicating other studies or were too similar to the ones chosen.

Results

Diagnosis

Various applications of nanoparticle technology have been found to be useful in diagnosing bone cancer. For example, Prashant Kesharwani et al. looked at the ability of gold-decorated nanodiamonds (GDNDs) to enhance Raman signals of several analytes when using an inelastic scattering behaviour known as Surface-enhanced Raman scattering (SERS) [9]. Raman signals are the outcome of inelastic light scattering by molecules. SERS is used to amplify the Raman signals of molecules to enhance molecule detection [9]. Raman signals allow for identification and structural analysis of molecules because they act as a chemical fingerprint. The authors found that photons reached higher levels of energy as soon as they interacted with the surface of nanoparticles [9]. The researchers modified the surface of the GDNDs and their shape to see how that impacted the amplification of the Raman signals of small molecules [9]. Their findings indicate that, based on the modifications that can be made, GDNDs can be used to amplify the signals of cancer-specific markers [9]. On the other hand, Yujing Guan et al. investigated the usefulness of another nanomaterial, carbon nanotubes, for diagnosing bone cancer [5]. They found that carbon nanotubes are useful in tumour cell imaging as they are able to transmit, store, and recover light wave signals [5]. In fact, TA Zdobnova et al. found that nanoparticles called quantum dots (QDs) could be used as fluorescent markers to detect and observe tumour markers *in vivo* as well as *in vitro* models [10]. QDs are semiconductor nanocrystals that exhibit distinct optical properties [10]. To ensure the QDs selectively bind to the specific tumour markers, these authors conjugated the QDs with a spectrum of targeting molecules, one of them being peptides [10]. The authors observed that QDs were able to accurately detect several tumour markers simultaneously with high sensitivity as well as specificity which makes them a useful tool to visualize tumours. Although it was also observed that the QDs accumulated in the organs of the reticuloendothelial system [10].

Treatment

The application of nanoparticles in bone cancer treatment has been studied *in vivo* and *in vitro*. Yifan Wang et al. used both *in vivo* and *in vitro* testing to determine that hydroxyapatite (the main mineral found in bone), in nanomaterial form with selenium ions incorporated into its structure could lead to apoptosis of bone tumor cells, while simultaneously promoting bone regeneration [11]. To determine the results, the authors used selenium-doped hydroxyapatite nanoparticles (Se-HANs) with various selenium concentrations of 3%, 6% and 10% [11]. For *in vitro* testing, human osteosarcoma cells were used while BALB/c nude mice with osteosarcoma tumors were used for *in vivo* testing [11]. The release of selenium from the Se-HANs stimulated the production of reactive oxygen species triggering caspase-dependent apoptosis [11]. In *in vivo* testing, reduced tumour weight and volume was noted [11]. While the selenium was used to kill the cancer cells, the hydroxyapatite of the Se-HAN component was noted to aid in repairing bone at the tumour removal sites [11]. Overall, the selenium and hydroxyapatite worked

together to inhibit the progression of osteosarcoma and help improve bone healing [11]. Similarly, Yongchun Liu et al. used both *in vitro* and *in vivo* testing to study the effectiveness of various palladium-based nanomaterials as photothermal agents in a cancer treatment called photothermal therapy [12]. The palladium-based nanomaterials were engineered to efficiently absorb near-infrared light, convert the light into heat, and then use that heat to create localized hyperthermia to ablate tumour cells without causing major side effects [12]. To improve the results of the photothermal therapy, the stability, blood circulation time, and tumour targeting ability of the palladium-based nanomaterials were enhanced by making surface and structural modifications [12]. Nobert Pardi et al. used only in vivo testing to examine effectively lipid nanoparticles (LNPs) delivered mRNA encoding firefly luciferase in mice [8]. The mRNA encoding firefly luciferase was encapsulated in LPNs [8]. The LPNs were administered to the mice in various ways which included intraperitoneal, intravenous, intradermal, subcutaneous, intramuscular, and intratracheal injections [8]. The LNPs were noted to be effective carriers for the delivery of mRNA which allowed for high levels of protein expression [8]. The levels of protein expression varied in location and duration based on the method that was used to administer the LNPs [8]. The authors determined that LNPs were safe to be used as a non-viral delivery method for mRNA therapies which include protein replacement therapies [8]. Likewise, Sandra Claveau et al. used *in vivo testing to study the*ability of hydrogenated detonation nanodiamonds (H-DNDs) to deliver small interfering RNA (siRNA) to Ewing sarcoma tumours in mice in order to reduce EWS-FLI1 oncogene expression [13]. The authors used H-DNDs as carriers for the siRNA that target the EWS-FLI1 oncogene in order to inhibit tumour growth [13]. They used detonation nanodiamonds labelled with tritium, a radioactive isotope of hydrogen, to track the distribution and elimination of the EWS-FLI1 oncogene [13]. When Ewing sarcoma tumours were implanted into nude micethey found that siRNA was efficiently able to reduce the EWS-FLI1 gene expression which led to a 50% decrease in tumors [13]. The authors also noted that although the nanodiamonds accumulated in organs and only a small amount of the nanodiamonds reached the tumour, the treatment was still successful in reducing the EWS-FLI1 oncogene expression [13].

Regeneration/Recovery

Nanotechnology is also useful to repair the damage to bones caused by bone cancer. In some cases, the bone tissue is regenerated with the help of nanoparticles, while, in other cases, nanoparticles are used to create scaffolds for reconstructing bone tissue. For example, calcium phosphate (CaP), is a ceramic nanoparticle made up of calcium ions and inorganic phosphate anions [14]. It is often used in nanotechnology during the post-treatment stage of bone cancer. Chrystalleni Hadjicharalambous et al. used CaP to deliver genes to promote bone regeneration [14]. They wanted to determine if using CaP nanoparticles containing plasmid DNA encoding human BMP-7, a bone morphogenetic protein, would induce an osteogenic differentiation in MC3T3-E1 pre-osteoblast cells [14]. Plasmid DNA encoding enhanced green fluorescent protein was used as the control to ensure the nanoparticles delivered the genes to the cells [14]. Polyethyleneimine was used to stabilize the CaP nanoparticles which were covered with a silica shell to protect the DNA component [14]. The nanoparticles were functionalized with thiol groups as well [14]. The authors investigated whether the CaP nanoparticles were able to transfect the cells and produce BMP-7 and, therefore, promote bone formation [14]. Hadjicharalambous et al. determined that osteogenic activity was enhanced due to an increase in deposition of calcium and the activity of alkaline phosphatase in the transfected cells [14]. The authors also concluded that this application did not adversely affect cell viability or proliferation, making it a temporarily safe, short-term gene therapy for bone regeneration [14]. In contrast,Ekaterina Chudinova et al., coupled CaP nanoparticles with 3-D printed Titanium-Aluminum-Vanadium (Ti6Al4V) alloy scaffolds to enhance the adhesion, proliferation, and osteogenic differentiation of human mesenchymal stem cells [15]. The Ti6Al4V scaffolds were coated with the CaP nanoparticles using electrophoretic deposition to increase the hydrophilicity of the scaffolds to make cell attachment more favorable [15]. The authors noted an improvement in osteogenic potential by an increase in alkaline phosphatase activity as well as increased mineralization [15]. This application allows for patient-specific treatments to be achieved as implants can be customized using 3-D printing along with nanoparticles [15]. Similarly, Tao Gong et al. discuss the ability of the nanostructure scaffolds to replicate the extracellular matrix (ECM) of natural bone [16]. The authors describe how scaffolds produced from hydrogel, nanofibers, nanoparticles, nanopores, and nanotubes have been used to mimic the ECM and replace defective tissues [16]. They note that nanotubes and nanopores have been used to improve vascularization and the diffusion of nutrients while the nanoparticles were used to enhance the mechanical strength of defective bone tissue [16]. Nanopatterns were used in the scaffolds to resemble the surface topography of the ECM in order to control stem cell differentiation, and nanofibres were used to mimic the look of the ECM's fibrous structure to stimulate osteogenesis [16].

Table 1. Summary of Articles Examining Nanotherapies for Bone Cancer

Application	First Author [Reference]	Nanomaterials Used	Major Findings
Diagnosis	Prashant Kesharwani [9]	Gold-decorate Nanodiamonds (GDNDs)	GDNDs can be used to amplify the signals of cancer-specific markers.
	Yujing Guan [5]	Carbon Nanotubes	Carbon nanotubes can transmit, store, and recover light wave signals for tumour cell imaging
	TA Zdobnova [10]	Quantum Dots (QDs)	QDs can accurately detect several tumour markers with high sensitivity and specificity.
Treatment	Yifan Wang [11]	Selenium-doped Hydroxyapatite Nanoparticles (Se-HANs)	Se-HANs stimulated the production of reactive oxygen species triggering caspase-dependent apoptosis which led to a decrease in tumour weight and volume.
	Norbert Pardi [8]	Lipid Nanoparticles (LNPs)	LNPs were safe and effective carriers for delivering mRNA therapies
	Sandra Claveau [13]	Hydrogenated Detonation Nanodiamonds (H-DNDs)	The H-DNDs efficiently delivered siRNA. The siRNA allowed for a reduction of the EWS-FLI1 gene expression which led to a 50% decrease in Ewing sarcoma tumours that were implanted into nude mice.
	Yongchun Liu [12]	Palladium-based Nanomaterials	The palladium-based nanomaterials efficiently converted near-infrared light to heat to create localized hyperthermia to ablate tumour cells.
Regeneration/ Recovery	Chrystalleni Hadjicharalambous [14]	Calcium Phosphate (CaP) Nanoparticles	CaP nanoparticles containing plasmid DNA encoding BMP-7 enhanced osteogenic activity in MC3T3-E1 pre-osteoblast cells.
	Ekaterina Chudinova [15]	Calcium Phosphate (CaP) Nanoparticles	CaP nanoparticles coupled with 3-D printed Ti6Al4V alloy scaffolds led to an improvement in osteogenic potential.
	Tao Gong [16]	Nanofibers, Nanoparticles, Nanopores, and Nanotubes	The materials have been used to mimic the ECM and replace defective tissues.

Discussion

Despite the promising results, many challenges remain in the use of nanotechnology for diagnosing, treating, and post-treatment recovery in relation to bone cancer. Although the nanocrystals, QDs, were noted to be useful in efficiently detecting cancer cells and the nanoparticles, H-DNDs, carried siRNA to treat cancer cells, both nanomaterials do accumulate in organs. The QDs were noted to accumulate in the reticuloendothelial system while the H-DNDs accumulated in organs such as the heart, kidneys, and lungs [10, 13]. Since nanoparticles tend to accumulate in bodily tissues, their elimination from the body can be quite slow depending upon the size of the nanoparticles being used [17, 18]. Unfortunately, there is some evidence that metallic nanoparticles can cause inflamed lungs and kidneys in rats [19]. Thus, although nanoparticles can be easily and accurately targeted, to the treatment area, problems can occur during the elimination of the nanoparticles from the body since they tend to accumulate in the liver, kidneys, spleen, and lungs which are the main organs involved in elimination of waste materials from the body [20]. In contrast, immune reactions are not considered a major issue with nanoparticle technology since most nanoparticles are too small to be detected by the immune system which would result in an immune response [21]. As well, nanoparticles can be engineered to avoid or target the immune system [22]. In fact, they have been found to be useful in suppressing the immune system when necessary [22]. Otherwise, only weak immune responses have been observed when using nanoparticles [21]. Further research would be needed to create effective methods to safely clear these nanomaterials from the body. Another challenge that is present when using nanotechnology is the uncertainty about the toxicity of the nanomaterials and how that would impact humans. As nanotechnology is still relatively new, more research is needed to fully understand their long-term safety and toxicity. In addition, researchers will need to learn more about the impact nanomaterials have on the environment to determine how much the nanomaterials should be incorporated into biomedical applications. For instance, Paresh Ray et al. point out that nanoparticles are so small that they can be easily breathed into the lungs and enter the lung's alveolar spaces which may lead to serious disease for humans and wildlife [3]. Cheng-Yu Jin et al. found that

increased concentrations of Titanium dioxide (TiO_2) nanoparticles in a culture medium resulted in higher levels of reactive oxygen species (ROS) [23]. ROS are molecules that contain oxygen and an accumulation of ROS could lead to DNA, RNA and protein damage in cells. In addition, Eun-Jung Park et al. [24] observed that nanoparticles can penetrate the plasma membrane and directly interact with cellular molecules resulting in harmful biological cell functions. If these challenges can be overcome, QDs will be an excellent tool as they are more advantageous than using traditional fluorophores because they are able to conduct multiplex imaging [10].

The most promising nanotechnology application is the replication of the body's natural process of bone tissue regeneration which would involve recruiting and differentiating progenitor cells [16] as closely as possible to help bones to form by mimicking natural bone regeneration involving the coupling of angiogenesis and osteogenesis. Recent research has shown the potential to create bone scaffolds that may result in localized or systemic functions [16]. Another area that shows potential is the use of nanotechnology to deliver drugs to improve the effectiveness of treatments already in place [8]. Since nanotechnology is a fairly recent field of study, more research is needed to determine the toxicity of various nanoparticles and the implications for the environment and human health resulting from either intentional or unintentional exposure. Furthermore, there are currently no uniform guidelines to follow when working with nanoparticles. Therefore, forming committees to study various aspects of nanoparticle use and free sharing of information would be very beneficial to guide researchers and medical practitioners. Likewise, standard dosing guidelines have yet to be established, so this is another area that needs to be researched and standardized. In addition, quality control and standardization in the production of nanoparticles does not yet exist since only a few nanomaterials are currently being produced in large batches [25] while other nanomaterials would still be produced in batches by individual laboratories as needed. Since nanotechnology is still in its infancy, there is much research needed to realize its full potential and to find ways of avoiding any dangers associated with the technology.

Conclusions

Although bone cancer is relatively rare, it is one of the more difficult to treat forms of cancer. Nanotechnology holds the potential to improve early diagnosis that would lead to more timely treatment of the disorder, potentially leading to a reduction in deaths. Moreover, nanotechnology shows promise for imaging, treating, and delivering various treatments to the site of tumours for more precise treatment that may result in less damage to surrounding cells. It has also been demonstrated that nanotechnology can be used to rebuild bones. Therefore, further development of nanotechnology for applications involving bone cancer show a great deal of promise.

List of Abbreviations

CaP: calcium phosphate
CT: computed tomography
ECM: extracellular matrix
GDNDs: gold-decorated nanodiamonds
H-DNDs: hydrogenated detonation nanodiamonds
LNPs: lipid nanoparticles
QDs: quantum dots
ROS: reactive oxygen species
Se-HANs: selenium-doped hydroxyapatite nanoparticles
SERS: surface-enhanced Raman scattering
siRNA: small interfering RNA
Ti6Al4V: titanium-aluminum-vanadium
TiO_2: titanium dioxide

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

No approval or consent was needed to complete this study.

Authors' Contributions

AM: performed conceptualization of the review, literature search, data extraction and analysis, interpretation of results, writing, and editing.

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