CHALLENGES AND INNOVATIONS IN SELECTED BIOMATERIALS FOR BONE CANCER THERAPY

Klaudia Malisz-Rudzińska [1], Beata Świeczko-Żurek [1*], Marcin Nowak [2]

[1] Department of Biomaterials Technology, Institute of Manufacturing and Materials Technology, Faculty of Mechanical Engineering and Ship Technology, Gdansk University of Technology, Poland, klaudia.malisz-rudzinska@pg.edu.pl, beata.swieczko-zurek@pg.edu.pl

[2] Department of Trauma Surgery and Orthopaedics, Hospital in Inowroclaw, Poland, marcinnowakmd@gmail.com

* Correspondence: beata.swieczko-zurek@pg.edu.pl

Abstract

Bone cancer remains a significant clinical challenge due to the high incidence and marked heterogeneity of malignant lesions affecting skeletal tissue. Current treatment strategies primarily aim to prolong patient survival and improve quality of life rather than achieve complete remission, while conventional therapies are often associated with substantial side effects. In recent years, biomaterial-based approaches—particularly polymeric and composite drug delivery systems in the form of scaffolds or bone cements—have emerged as promising alternatives. These platforms enable localized therapeutic delivery and can be synergistically combined with magnetic hyperthermia or photothermal therapy to enhance anticancer efficacy. Moreover, many such materials exhibit antibacterial properties, offering additional protection against postoperative infections. This review examines the key challenges and recent advances in biomaterial-based strategies for the treatment of primary bone cancers and bone metastases, encompassing both conventional therapeutic approaches and emerging multifunctional material systems.
Keywords: *bone cancer, bone metastases, biomaterials, drug delivery, photothermal therapy, magnetic hyperthermia.*

Introduction

Bone is a highly dynamic and active connective tissue that protects essential organs, provides mechanical support, mobility, and the structural framework of the body [1]. It is also particularly important for the metabolism of minerals [2]. Although bone has a significant potential for regeneration and functional stability. However, in the case of critical defects caused by a tumor, trauma, or infection, the ability of the bone tissue to heal itself is compromised. Specifically, bone is a common location of metastasis for cancer patients and is also linked to the occurrence of infrequently occurring malignant primary tumors [1]. Many approaches have been developed to improve healing, including primarily surgical approaches, for example, methods to increase mechanical stability, debridement at the fracture site, and the delivery of graft material to enhance healing. Up to 5-10% of fractures show delayed or complete failure to heal despite currently available healing aids. Therefore, developing methodologies to promote bone healing is an important research topic [2].

Bone metastases are common and usually indicate a poor prognosis for cancer patients. Most bone metastases are caused by prostate and breast cancer. Particularly in adults, bone metastases are much more common than initial bone malignancies. Less common are primary bone tumors such as osteosarcomas, chondrosarcomas, and Ewing sarcomas [1,3,4]. However, the treatment methods used have their limitations, and scientists are faced with the need to refine and develop new therapies.

Numerous biomaterials have been developed as innovative solutions for the local delivery of chemotherapeutics (e.g., polyethylene glycol (PEG), polyvinyl alcohol (PVA), polymethyl methacrylate (PMMA), chitosan (CS), alginate, cellulose, etc.), hydroxyapatite, and composite scaffolds. Besides, scientists also use magnetite-based materials for hyperthermia treatment or nanomaterials with strong near-infrared (NIR) light absorption, e.g., gold nanoparticles, carbon nanomaterials, copper nanomaterials for photothermal therapy, as well as smart multifunctional materials provided with both structural and therapeutic properties [5–7]. Cemented reconstruction procedures are often employed, in which PMMA bone cement is used as an adjuvant to bone reconstruction to reduce postoperative complications. Numerous studies have been reported in the literature on the use of bone cement as a carrier for chemotherapeutic drugs to prevent tumor recurrence [8]. Additionally, antibacterial materials can also be used to prevent postoperative infections [9].

The purpose of this review is to describe current proposals for innovative materials for the treatment of bone metastases and primary bone cancers. The issues of bone cancer and the more common bone metastases are discussed. Both conventional therapies and the latest scientific proposals are presented.

Bone Cancer

Bone tumours include primary bone tumours (sarcomas) and secondary bone tumours (metastases). The most common sarcomas are osteosarcomas (35%), chondrosarcomas (25%), and Ewing sarcomas (16%) [1,10]. Although these cancers are relatively rare and account for less than 1% of all cancer diagnoses each year, they are associated with significant mortality [11]. In England, the 10-year survival rate for bone sarcoma was 55% (2009–2013). It was also reported that the incidence of bone sarcoma in the UK is highest among individuals aged 75–79 years (2016–2018), with the lower limb being the most commonly affected site [12]. Bone metastases are diagnosed much more frequently.

Generally, metastases are the most common cause of cancer-related death. Metastasis is a multistep process that begins with the loss of intercellular cohesion, followed by tumour cell invasion into the vascular lumen, survival in circulation, and evasion of local immune responses. Finally, the cells extravasate from the intravascular space and proliferate in distant organs [3,13]. Bone metastases most often result in a short-term prognosis for an oncology patient. The spread of cancer to the bone limits the possibility of a cure, but its growth can often be slowed. Prostate and breast cancer are responsible for approximately 70% of bone metastases [3]. Bone metastases are often the cause of death, characterized by severe pain, limited mobility, spinal cord compression,

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disease-related fractures, bone marrow failure, and hypercalcemia [3,14]. In the case of breast and prostate cancer, the anticipated survival of patients following a diagnosis of bone metastases is typically no longer than two to three years[15,16]. In the case of advanced disease, the incidence of bone metastases in patients with both breast and prostate cancer is 65 – 75%, for lung cancer it is 30 – 40%, thyroid tumor 60%, and the lowest value is characterized by melanoma 14% but to 45% [3,11]. Bone metastasis is common in pediatric cancers, particularly in children with neuroblastoma, osteosarcoma, and Ewing sarcoma [15]. The treatment of bone cancer requires a multidisciplinary approach, involving various specialists such as surgical oncologists, medical oncologists, and radiation oncologists. The treatment process will depend on many factors, including the histological type of the cancer, location, extent, grade, and presence of metastases. Treatment options consist of surgery, especially limb salvage surgery, chemotherapy, and radiation [17]. In patients with osteoblastic lesions and pain syndrome, radionuclide therapy is advised for pain relief. High radiation doses are targeted at bone metastases and micrometastases in the bone marrow using low-energy beta-emitting radionuclides such as Samarium-153 ethylene diamine tetramethylene phosphonate (EDTMP) and ^{89}strontium. The response rate for pain syndrome is approximately 75%, with around 25% of patients potentially becoming pain-free [18].

Osteosarcoma is a malignant tumor that arises from mesenchymal tissue, representing up to 20% of all primary malignant bone tumors globally. It is the most common primary bone tumor in children and young adults. Unfortunately, it is characterized by high invasiveness, rapid progression of the disease, and very high death rate [19,20]. Standard treatment involves a combination of cisplatin, doxorubicin, methotrexate, and/or other drugs, followed by either limb-sparing surgery or amputation. Unfortunately, approximately 30% of patients are resistant to treatment, and the 5-year survival rate for recurrent or metastatic osteosarcoma is less than 25% [5]. Chondrosarcoma is a neoplasm that forms cartilage. The World Health Organization (WHO) has classified cartilage tumors into groups: benign, intermediate (locally aggressive or rarely metastasizing), and malignant. Unfortunately, most chondrosarcomas do not respond to chemotherapy and radiotherapy, making treatment options for patients with metastatic or unresectable chondrosarcomas limited [21,22]. Whereas, Ewing sarcoma and Ewing-like sarcomas are very aggressive bone and soft-tissue cancers, primarily affecting children and young adults. At the time of diagnosis, this disease is most often characterized by micrometastases. The current standard of patient care involves administering multiple cycles of systemic therapy alongside local treatment. However, the combination of non-targeted chemotherapy and constantly advancing local treatments now provides a realistic chance of cure for most patients with Ewing sarcoma [23,24].

Biomaterials

Treatment methods for bone cancer remain limited because they cannot effectively eradicate cancer cells. Current therapies focus on achieving local tumor control through surgical resection or radiotherapy, followed by pharmacological treatment. Unfortunately, chemotherapeutic agents act indiscriminately, resulting in damage to healthy tissues alongside cancer cells [25]. Palliative treatment is also frequently applied, aiming to improve quality of life by reducing pain rather than permanently curing the disease. Precision medicine and nanomedicine offer new approaches to cancer therapy, creating opportunities for targeted treatment and effective drug delivery to bone cancer sites [5,26]. The medicines such as cisplatin, doxorubicin, and methotrexate are often used [5]. Scientists are increasingly using nanomedicine to enhance the effectiveness of cancer therapies while reducing systemic toxicity [27]. Nanotechnology has allowed the development of new treatment options for bone cancer. Innovative methods are based on functional biomaterials and combine cancer therapy and bone regeneration. The bone cancer treatment and related issues are often discussed by scientists, and subsequent ongoing research gives great hope for finding the most effective therapy. The development of new complementary or alternative biomaterial-based cancer treatments may avoid these side effects by selectively delivering the pharmaceutical to a specific target [7].

A newer treatment modality is photothermal therapy (PTT), which is effective for localized tumor treatment because focused laser irradiation targets a specific area, allowing heat to penetrate deeply while minimizing damage to surrounding organs and tissues. It involves the conversion of near-infrared (NIR) light into localized thermal energy to eliminate cancerous tissue. For this purpose, nanomaterials with strong NIR absorption can be used, such as gold or magnetic nanoparticles, as well as carbon- and copper-based nanomaterials [7].

Hydroxyapatite

Hydroxyapatite (HAp) is a widely used bioceramic that is biocompatible, bioactive, osteoconductive, nontoxic, and noninflammatory. It is frequently applied in contact with bone tissue due to its similarity to bone mineral, and its high chemical stability leads to slow degradation, which influences osteogenesis, angiogenesis, and clinical applications [28–32]. Nanostructured hydroxyapatite is one of the promising nanocarriers and has found application as an antibacterial agent or drug delivery system [33]. The incorporation of various additives can improve both the physicochemical and biological properties of hydroxyapatite, enabling its use in biocomposites [34]. Elements such as magnesium, strontium, silicon, and zinc have been added to HAp to stimulate osteogenesis and reduce inflammation [35]. Wang R. et al. [6] investigated the effect of nano-HAp on osteosarcoma cell proliferation. They synthesized nano-HAp and, using a BALB/c nude mouse tumor model, demonstrated that nano-HAp effectively inhibited tumor growth *in vivo*. It was also confirmed that HAp nanoparticles limited the migration and invasion of osteosarcoma cells *in vitro* [6].

Because the concentration of cytostatics in the tumor is insufficient, complicating the systemic pharmacological treatment of bone tumors, it is crucial to develop advanced, localized drug delivery systems. Liu Y. et al. [36] demonstrated that doxorubicin (DOX) in combination with hydroxyapatite. Hydroxyapatite nanoparticles functionalized with DOX are absorbed into the lysosomes of osteosarcoma cells. The acidic microenvironment present there leads to the breakdown of the bond between the pharmaceutical and HAp. The released substance accumulates in the mitochondria, leading to cell starvation, decreased migration, and apoptosis. The therapeutic delivery system was evaluated *in vivo* using mice with osteosarcoma. The study demonstrated that the locally administered drug using HAp had a more potent tumor eradication effect than the control group. This suggests that beyond systemic chemotherapy, HAp nanoparticles could be used as a vehicle for intracellular delivery of doxorubicin to prevent tumor relapse following surgical resection in osteosarcoma [36]. The same medicine was used by Kang N.-W. et al. [37]. They developed self-assembled DOX-loaded alendronate-decorated human serum albumin (HSA-AD) nanoclusters (NC) for effective bone tumor-targeted therapy.

The ability to target bone tumors was tested using a cell culture and mouse model incorporating hydroxyapatite beads, which mimic the bone tumor microenvironment. The ability of targeted therapy significantly improves therapeutic efficacy in mice with bone tumors. Therefore, it can be concluded that the proposed solution will be a promising drug delivery system for the treatment of bone tumors [37].

Xu D. et al. [38] fabricated biomimetic multifunctional composite microparticles by incorporating the amphiphilic prodrug of curcumin with hierarchically structured HAp microspheres. The material's physicochemical properties were analyzed, and the composite's anti-osteosarcoma effect was evaluated. Flake-shaped, hierarchically structured HAp microspheres exhibited a high loading capacity and improved the stability of the cargo. Moreover, cancer cells showed over 3 times better uptake of this type of flake microspheres, which promotes the targeted antitumor activity of the prodrug. Studies have shown that biomimetic multifunctional composite microparticles inhibit tumor growth and metastasis by inducing apoptosis and preventing cell proliferation and tumor blood vessel formation. It may be used to develop an effective platform for targeted therapy [38]. However, Ram Prasad S. et al. [39] proposed hydroxyapatite-poly(vinyl alcohol) core-shell nanoparticles for the combined delivery of methotrexate and gemcitabine in the treatment of bone cancer. They used HAp nanoparticles as a core and poly(vinyl alcohol) (PVA) as the corona. Cell viability assays using osteosarcoma MG-63 cells demonstrated that polymer-coated nanoparticles were non-cytotoxic, while the drug-loaded nanoparticles displayed cytotoxicity in a dose-dependent manner. This means that the produced material is an effective therapeutic delivery system for the treatment of bone diseases [39].

Zhang G. et al. [40] designed a new multifunctional scaffold material, primarily made of hydroxyapatite nanoparticles, MXene nanosheets, and g-C_3N_4, to inhibit tumor recurrence and enhance bone formation. The composite scaffold exhibits remarkable photothermal and photodynamic properties. This enables the use of photothermal therapy, which is applied in cancer treatment due to the lower heat resistance of cancer cells. It has been found that nano-HAp further enhances the synergistic anti-tumor effects of both photodynamic and photothermal therapies, and the scaffold is capable of eliminating osteosarcoma cells within just 10 minutes at a temperature of 45 °C. Additionally, it shows cytocompatibility and has the potential to induce osteogenic differentiation of bone marrow stem cells. Given these findings, this material could be used for treating tissue damage following bone tumor resection [40]. The literature indicates that magnesium-doped wollastonite bioceramic material possesses strong mechanical properties and biological activity, making it highly promising for repairing bone defects. This is why Shao H. et al. [41] used those materials to fabricate magnesium-doped wollastonite/nano-HAp bioceramic scaffolds with precise porous frameworks using 3D printing and deposition methods. Research demonstrated that the bioceramic scaffold produced with a coating thickness of 15 μm displayed the most superior mechanical properties. It was noted that the nanohydroxyapatite coating effectively prevented the proliferation of human osteosarcoma cells, while the scaffolds promoted the osteogenic potential of rat bone marrow stem [41]. Another design of scaffolds for the treatment of malignant bone tumors. Dai W. et al. [42] created polyetherether-ketone (PEEK) scaffolds modified with molybdenum disulfide (MoS_2) nanosheets and HAp nanoparticles using a hydrothermal technique. It was observed that MoS_2 has good stability and a high NIR absorbance, so it could be ideal for PTT. *In vitro* experiments revealed that the viability of MG63 osteosarcoma cells is notably decreased when modified PEEK scaffolds are exposed to NIR irradiation. The incorporation of HAp nanoparticles into the material promotes cell proliferation and attachment, enhancing mineralization to facilitate bone defect repair. The addition of HAp was essential due to PEEK's low biocompatibility and inert nature [42]. Another proposal for treating osteosarcoma and supporting bone regeneration was proposed by Huang H. et al. [43]. They also considered that the key factors in treatment were the total eradication of the cancer, repair of the resulting bone defects, and prevention of bacterial infections. For this purpose, they synthesized selenium/strontium/zinc-doped hydroxyapatite powder using the hydrothermal method and subsequently combined it with polycaprolactone as ink to fabricate composite scaffolds via 3D printing. The material was applied in the repair of bone defects caused by malignant osteosarcoma. The added components improved the anti-tumor, osteogenesis, and anti-bacterial properties of hydroxyapatite. Studies indicated that the scaffolds were effective for tumor therapy, bone defect repair, and post-surgical infection prevention. This makes it a promising therapeutic material for osteosarcoma [43].

Graphene and its composites find applications in sensors, implantology, and gene and drug delivery. Graphene sheets are particularly useful in areas such as bacterial inhibition, cancer targeting, cellular imaging, antiviral material development, and tissue engineering. In tissue engineering, graphene is commonly incorporated into composite materials and scaffolds, often combined with hydroxyapatite or chitosan to form biocompatible composites [44,45]. Graphene-based polymer nanocomposites have recently enhanced polymers' thermal, electrical, and mechanical properties. Li X. et al. [45] fabricated graphene oxide/ silk fibroin/ hydroxyapatite nanocomposite membranes using the biomimetic mineralization process and one-step vacuum filtration. The 2D membrane was designed to exhibit both mechanical strength and flexibility while supporting cell adhesion for bone regeneration. Two-dimensional materials are crucial for bone regeneration as they create a controlled environment for the process and protect surrounding tissues. The mechanical strength of the membranes and the hydrophilicity of the surface were enhanced by the presence of hydroxyapatite and silk fibroin. A small amount of Hap enhanced osteoblast adhesion, differentiation, and mineralization. Studies indicated that nanocomposite membranes with a porous structure possessed distinctive mechanical properties and demonstrated potential for bone regeneration [45]. Furthermore, Megha M.et al. [46] also incorporated hydroxyapatite with additives in tissue engineering. They employed the wet precipitation method to synthesize vanadium (V) and yttrium (Y) co-doped HAp bio-ceramics. These additives were used because vanadium promotes osteogenesis and antibacterial properties, while yttrium enhances the stability and surface properties of the biomaterial. Yttrium also has potential in cancer treatment and radioactive imaging diagnostics. It was observed that doping pure HAp with V and Y improved its porosity, hemocompatibility, and mechanical properties. Additionally, the resulting material exhibited increased antibacterial activity against *P. aeruginosa and S. aureus* [46]. Another suggestion is to add selenium (Se). Barbanente A. et al. [35] used Se-doped hydroxyapatite nanoparticles as a promising therapy for bone tumors. The materials were synthesized using a novel and mild wet method. *In vitro* cell tests demonstrated that Se-doped hydroxyapatite nanoparticle suspensions with a low Se concentration showed good cytocompatibility. However, a high concentration of Se exhibited strong cytotoxic activity against cancer [35].

Chitosan

Chitosan (CS) is a biopolymer obtained from naturally occurring chitin. Chitin, in turn, is sourced from the exoskeletons of crustaceans as well as from the cell walls of fungi and insects. CS has received significant attention due to its antimicrobial activity, adhesiveness, biocompatibility, and complete biodegradability, in combination with low toxicity, hemocompatibility, protein adsorption capability, chemical stability, and its ability to promote wound healing [47–54]. It is employed in biomedical devices and implants, primarily due to its ability to enable controlled drug release [48]. However, pure CS exhibits weak mechanical properties, low porosity, and a low swelling ratio. Since these characteristics are often insufficient, they can be improved by adding various additives [55]. Due to its unique properties, chitosan is extensively used in bone repair applications. When compared to synthetic materials like polycaprolactone and polylactic acid, the hydrophilic nature of CS enhances cell adhesion and growth on scaffold surfaces [56].

Chitosan has been used in scaffold form to enhance fracture repair efficiency. It serves as a delivery system for growth factors such as platelet-derived growth factor, fibroblast growth factor, insulin-like growth factor, and tumor growth factor β to mesenchymal stem cells [48]. Additionally, chitosan-based scaffolds can function as carriers to effectively regulate the release of osteo-inductive molecules, including drugs [50,56]. Amini Z. et al. [57] proposed a chitosan-based material for controlled drug release at different pH levels and temperatures for the treatment of bone cancer. They developed chitosan-grafted poly(ε-caprolactone) nanofibers by electrospinning and incorporated magnetic bioactive glasses/cisplatin into the nanofibers. It is well established that magnetized bioactive glasses applied in hyperthermia cancer treatment can enhance therapeutic efficacy in tumorous bone by eliminating cancer cells at approximately 43 °C (mild hyperthermia). Thus, magnetic bioactive glasses may represent a promising alternative for cancer treatment by integrating chemotherapy (controlled drug release) with hyperthermia. The resulting nanofibers were evaluated using MG-63 osteosarcoma cells and demonstrated controlled cisplatin release without an initial burst. Moreover, nanofibers at a concentration of 100 μg/mL were found to be optimal for killing MG-63 cells through the combined effects of chemotherapy and hyperthermia [57]. Chitosan has also been used for the delivery of doxorubicin in the treatment of osteosarcoma [58]. In addition, it has found applications in immunotherapy. The cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway, which is crucial for DNA sensing, regulates both innate and adaptive immune responses and plays a significant role in tumor immunotherapy [59].

Often, improving the properties of pure CS scaffolds is achieved by using mineral and bioactive ceramics such as hydroxyapatite. CS/HAp scaffolds show promise in use as bone scaffolds [55]. Despite numerous advantages, chitosan/hydroxyapatite scaffolds have some limitations, e.g., low porosity volume, large pore sizes, and an uneven distribution of the HAp phase within the polymer matrix. However, those problems can be overcome by incorporating a third additive into the material. Various substances can be used for this purpose, including Ag, cellulose, magnetic particles, graphene oxide, alginate, and Zn [55]. Abdian N. et al. [55] used this kind of modification and prepared chitosan/ hydroxyapatite/ mesoporous SiO_2-HAp scaffolds by the freeze-drying technique, intended for use as an implant for injured bones and as systems for drug delivery. Studies have shown that pure chitosan cannot provide appropriate implant properties in bone tissue engineering, but its modification significantly improved the material properties. CS/HAp/SiO_2-HAp scaffolds, characterized by small pores and high surface area, are capable of storing drugs for prolonged periods and releasing them gradually. Additionally, scaffolds with tramadol (an analgesic with a short half-life used to manage pain) can be effectively used as an implant to regenerate injured bones and provide targeted drug delivery to adjacent tissues [55]. Lu Y. et al. [60] have also been working on biomaterials that combine tumor-suppressing and bone-healing properties to address the significant bone damage and high likelihood of local recurrence after initial surgery for bone cancer treatment. Bisphosphonates are a type of small-molecule drug and are commonly used in the treatment of cancer bone metastases. The chosen zoledronic acid is a third-generation bisphosphonate that prevents osteolysis and restores bone density in specific bone erosion conditions. Due to its strong affinity for bone tissue, the medicine accumulates in them, reducing its distribution to healthy tissues [61]. Lu Y. et al. [60] prepared a high-activity chitosan/nanohydroxyapatite scaffold containing zoledronic acid (CS/nHAp/Zol). The obtained scaffolds exhibited excellent tumor inhibition properties towards giant cell tumors of bone *in vitro*, promoting cell apoptosis by enhancing the expression of pro-apoptosis genes and decreasing the osteoclastic activity of cancer cells by down-regulating osteoclast genes. Moreover, the materials had good biocompatibility and osteoinductivity and presented antibacterial activity against *S. aureus* and *E. coli* [60].

Given the persistent issues of complications following bone tumor resection, such as cancer recurrence, infection, and significant bone loss, Zhao Y. et al. [9] also created proposals for the scaffold. They introduced a chitosan/hydroxypropyltrimethyl ammonium chloride chitosan/hydroxyapatite/ black phosphorus hybrid photothermal scaffold. Research has demonstrated that under the influence of NIR irradiation, the scaffold can eradicate 95% of osteosarcoma cells, along with 97% of *E. coli* and 92% of *S. aureus*. Additionally, mild hyperthermia stimulation (~42 °C) effectively promotes osteogenesis by enhancing the expression of heat shock proteins [9]. He M. et al. [62] also proposed scaffolds for osteosarcoma management and bone repair. They developed a multifunctional composite coating based on layer-by-layer assembled black phosphorus nanosheets/chitosan (BP-NS/CS), which was deposited onto a 3D-printed PEEK bone scaffold. The presence of CS was found to effectively protect black phosphorus nanosheets from rapid degradation. In addition, the composite coating, incorporating BP as a photothermal agent, facilitates cancer treatment through multimodal therapy by combining laser-induced heating with pH-sensitive drug release. Moreover, reactive oxygen species released by BP-NS reduce the risk of postoperative infection by eliminating bacteria such as *E. coli* and *S. aureus*. Furthermore, studies demonstrated that the composite coating enhanced scaffold biocompatibility and promoted the expression of osteogenesis-related genes [62].

Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) possess a high specific surface area, exhibit excellent biocompatibility, and can be easily surface-modified, making them suitable for use in drug delivery systems [5,61]. The material's porous structure enables drug loading and can be modified with additional molecules. To improve release efficiency, the pore gate can be activated at the target site by a specific stimulus (such as temperature, enzyme, light, or pH). MSNs, which are pH-sensitive, are among the promising carriers for delivering anticancer drugs to the intended location [5].

Sum W. et al. [61] prepared a bone-targeted nanoplatform, which was created by incorporating gold nanorods within silica nanoparticles (Au@MSNs), which were conjugated with zoledronic acid. Their studies showed that the designed nanoparticles could target bone *in vivo* and also prevent the formation of osteoclast-like cells and stimulate osteoblast development *in vitro*. Additionally, the combination of Au@MSNs-ZOL and photothermal therapy effectively reduced tumor growth both *in vitro* and *in vivo*, while also alleviating pain and bone resorption *in vivo* by inducing apoptosis in tumor cells and enhancing the bone microenvironment. This material, which integrates ZOL and PTT, could be applicable for the treatment of bone metastases caused by breast cancer [61]. Furthermore, Martínez-Carmona M. et al. [63] developed a multifunctional nanodevice exhibiting selective activity toward human osteosarcoma cells while enabling pH-responsive delivery of antitumor drugs. Their approach was based on doxorubicin-loaded MSN nanoplatforms functionalized with polyacrylic acid and a target-specific ligand, the plant lectin concanavalin A. *In vitro* studies showed that internalization of lectin-conjugated nanosystems by human osteosarcoma cells was approximately twofold higher than that observed in human preosteoblastic cells. In addition, 100% antitumor efficacy against osteosarcoma cells was achieved at low DOX concentrations. These results suggest the significant potential of this material for bone cancer treatment [63]. Gao J. et al. [64] proposed a tri-responsive dual-drug delivery system for the treatment of osteosarcoma. In their project, methotrexate was encapsulated within mesoporous silica nanoparticles using polydopamine (PDA), and the resulting core-shell structured MTX/MSNs@PDA was integrated into graphene oxide nanosheets to further improve the photothermal conversion efficiency of the system. As the second medicine, naringin is co-encapsulated with MTX/MSNs@PDA@GO by the carboxymethyl cellulose/cystamine hydrogels. Both PDA and GO in the developed material serve as excellent photothermal agents, allowing for an optimal response to NIR radiation. Studies have shown that the developed tri-responsive dual-drug delivery system can be used in chemo-photothermal therapy of osteosarcoma, and the cell viability under NIR irradiation is less than 10% [64]. Besides treating bone cancer and bone metastasis, mesoporous silica nanoparticles are also used as carriers for antibiotics to combat infections, as well as for regenerating bone defects and treating osteoporosis [65–67]. Moreover, it has been reported in the literature that ultrasmall nanoparticles within rod-shaped mesoporous silica nanoparticles have been applied in cancer diagnostic imaging using 3D tomography [68].

Black bioceramics

Black bioceramics exhibit outstanding photothermal antitumor effects in both skin and bone tumors. At the same time, they can significantly enhance bioactivity for skin and bone tissue repair *in vitro* and *in vivo* [69]. Black phosphorus exhibits favorable biocompatibility and physicochemical properties, which have led to significant advances in basic research and biomedical applications. Its structural anisotropy confers remarkable properties, including electrical conductivity, topological characteristics, and optical and mechanical performance. As previously mentioned, it has also been investigated for therapeutic delivery, high drug-loading efficiency, and excellent photodynamic and photothermal properties [70].

Rucci M. et al.[71] evaluated the use of few-layer two-dimensional black phosphorous (2D BP) as a potential option for osteosarcoma therapy. Their study indicated that the presence of two-dimensional black phosphorous reduces the metabolic activity of osteosarcoma cells and stimulates the proliferation and osteogenic differentiation of human preosteoblast cells and mesenchymal stem cells. Additionally, 2D BP may enhance the production of anti-inflammatory cytokines and suppress the synthesis of proinflammatory mediators, thus suggesting the opportunity to reduce cancer-induced inflammation [71]. However, Qin L. et al. [72] introduced a material for chemo-photothermal combination therapy to treat cancer. They examined a thermosensitive hydrogel containing black phosphorus nanosheets and gemcitabine. The results indicated that the phase translation of the hydrogel was near body temperature, and the material exhibited excellent photothermal efficiency *in vitro*, along with good biodegradability. This suggests that the combination of photothermal therapy and chemotherapy enhanced the antitumor effect [72].

The use of chemotherapy combined with PTT in cancer treatment remains a highly promising area of research. Therefore, Luo M. et al. [73] developed a light- and pH-sensitive nanoparticle based on black phosphorus quantum dots (BPQD) for targeted chemo-photothermal therapy. For this purpose, doxorubicin was used. The results show that the obtained nanosystem had outstanding photothermal performance both *in vitro* and *in vivo*. The combination with folic acid provided this system with exceptional cancer-targeting effects. The BPQDs-based drug delivery system displayed pH- and photo-sensitive release properties, minimizing potential harm to normal cells. This system, sensitive to both pH and light, was designed to reduce the risk of damage to healthy cells [73].

Bone cements

Bone cements are biomaterials created by mixing a powder with a liquid phase. They can be applied and implanted in a paste-like form and subsequently bond once introduced into the body [74]. Polymethyl methacrylate (PMMA) cement is a widely used bone substitute in orthopedic procedures [75]. PMMA is designed to provide mechanical support to weakened bone, thereby relieving pain caused by fractures associated with bone cancer [76]. However, due to its dense structure, PMMA is not suitable for the local delivery of chemotherapeutic drugs to prevent tumor recurrence [75].

Wang Z. et al. [75] modified PMMA bone cement to improve its properties and local delivery of chemotherapeutic drugs. They introduced porosity into PMMA cement by incorporating carboxymethylcellulose (CMC). The results indicated that the mechanical strength of PMMA-based cements decreases progressively as the CMC content increases. They confirmed the chemotherapeutic activity of the released medicine from the obtained cement [75].

Another approach involves using hyperthermia treatment with magnetic bone cement. Magnetic bone cements contain magnetic particles that are distributed in the cement matrix. Hyperthermia therapy aims to eliminate tumors by raising the temperature, based on the principle that cancer cells are much more sensitive to heat than healthy cells due to the abnormal blood vessel network in tumors [77–79]. Zhao S. et al. [77] demonstrated a super-paramagnetic injectable, degradable, radiopaque bone cement (MSBC). To obtain the injectable MSBC, they incorporated SiO_2-modified nano Mn-Zn-Cu-Gd ferrites into an acidic calcium phosphate cement matrix. *In vitro* studies indicated that the cement can achieve self-controlled hyperthermia around a Curie temperature of 65 °C when exposed to an alternating magnetic field. Besides, the non-cytotoxic cement showed good cell affinity, and it enhanced the mineralization ability of osteoblasts [77]. Liang B. et al. [76] proposed a different material for synergistic magnetic hyperthermia ablation combined with chemotherapy of osteosarcoma. They developed a multifunctional bone cement loaded with Fe_3O_4 nanoparticles and doxorubicin (DOX/Fe_3O_4@PMMA) [76]. Fe_3O_4 nanoparticles are described as a mediator for the conversion of magnetic energy into thermal energy

[76,80]. The developed bone cement was characterized by the controlled release of the antitumor drug, promoting the apoptosis of abnormal tissue, and inhibiting the proliferation of osteosarcoma cells. Importantly, research has demonstrated that the Fe_3O_4 nanoparticles do not migrate into the surrounding tissues [76]. Lei Q. et al. [81] took a different approach by using magnetic bioglass. They prepared the highly porous magnetic bioglass using a sol-gel method and then compounded it with calcium sulfate bone cement to form the composite scaffold (CS-MBG). The scaffold released Ca^{2+}, leading to cell death due to calcium overload. Additionally, the pH and osteogenic activity of the prepared composite can support bone repair and suppress the growth of bone tumors. Furthermore, it was established that the right amount of Fe_3O_4 addition ratio could create effective encapsulation during the bioglass synthesis, resulting in the maximum magnetothermal therapeutic effect [81].

Conclusions

Biomaterials have garnered increasing interest due to their unique biological properties, excellent cancer specificity, high drug-loading capacity, and controlled release. Biomaterial scaffolds closely mimic native tissue and are biocompatible, non-toxic, and unlikely to induce inflammatory or immunological responses, allowing their safe use in patients. Researchers continue to develop functional biomaterials that not only selectively and synergistically target cancer cells but also repair bone defects resulting from surgical resection while providing antibacterial activity. This review presents numerous proposals for materials with dual or triple functionality. However, further research and innovative solutions are still needed to achieve optimal anticancer efficacy and adequate bone regeneration.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve the style of selected fragments of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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