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A REVIEW ON EMERGING THERAPY OF CANCER

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Abstract:
Every year, cancer kills millions of people throughout the world, and despite significant advances in medicine, there are still many difficulties that need to be addressed in order to enhance cancer treatment. As a result, oncological research is focusing its efforts on developing novel and effective therapies that can mitigate the negative effects of current treatments. Various technologies are now being tested in clinical trials or have previously been implemented in clinical practise. Bioengineering of extracellular vesicles and cells derived from patients has permitted the development of ad hoc systems and univocal targeting tactics, while nanomedicine contributes to the production of biocompatible materials for diagnostic and therapeutic applications. We will examine the most innovative advances in basic and applied cancer research in depth in this review.

Key words:*Cancer, Therapy, Diagnostic, Therapeutic applications*

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INTRODUCTION: [1,2]

Breast cancer (BC) is the most common malignant tumour among women [1]. According to the American Cancer Society (ACS) reports, BC leads to the second-highest cancer-related deaths in women after lung cancer. One in 38 women (about 2.6%) will die from BC. There were 2.3 million new cases in 2020 that led to 685,000 deaths globally. In addition, the ACS pointed out that BC's incidence rate increased about 0.3% per year in recent years. The mortality rate also increased significant from 1990–2015. Based on the immune histochemical expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), BC can be classified into four major subtypes: hormone receptor (HR)+/HER2+, HR+/HER2−, HR−/HER2+ and HR-/HER2−[2].

According to the molecular profiles, BC could be classified as luminal subtype, HER2 enriched+ subtype, and basal-like subtype with a high expression of basal markers. The luminal subtype could be divided into luminal A and luminal B tumours. The luminal A that comprises 40% of all subtypes shows the best clinical prognosis with a high level of ER expression. Therefore, these patients are more likely to benefit from hormonal therapy alone. The other less common subtype, luminal B (20%) tumours, express ERs at a lower level but exhibit higher levels of proliferation-related genes. Consequently, patients within this category may need chemotherapy. HER2 enriched tumours (15%) also show overexpression of proliferation-related genes. HER2+ tumours that are ER- are classified as luminal B subtype [3].

The basal-like group is characterised by the upregulation of genes expressed by basal/myoepithelial cells. Although it has been reported that 71% of TNBC tumours were found to be basal-like and 77% basal-like tumours were triple negative, TNBC and basal-like BC are not synonyms. TNBC can be further divided into six subtypes: basal-like (BL1 and BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory(IM),andluminalandrogenreceptor (LAR),andanunspecifiedgroup (UNS) [4].

Metastasis is one of the main reasons for the high mortality rate among BC patients. About 20–30% of recurrences among early BC patients are accompanied by metastatic diseases . Common metastatic sites for breast cancer are bones, liver, lungs, and brain . According to recent research, bone is the most common metastatic organ, while the brain is the least. In addition, different subtypes of BCs have variable likelihoods of developing metastasis. For example, the HER+ BC and TNBC are more aggressive and more likely to develop metastasis . Some studies indicate that bone metastases are more frequent in HR+ subtypes than all other BC subtypes. Bone metastasis influences the quality of patients' life by inducing skeletal-related events (SREs), such as bone pain and tumour-induced fracture, and decreases survival. The average five-year survival rates for the patients with local-regional and metastatic recurrence are 80% and 25%, respectively [5].

Mechanism of BC Bone Metastasis:

The BC metastasis process includes several complex steps: invasion, migration, adhesion, and survival of the tumour cells at the metastatic sites. The "seed and soil" theory was first reported in 1889. This means the development of cancer metastasis depends on theinteractionsbetweenthe"seeds",whichindicatethetumourcells,andthe"soil",which suggests the microenvironment of the potential metastatic site [6].

Invasion:

In metastasis development, BC cells at the primary tumour site first induce angiogenesis to ensure they have access to nutrients for proliferation. The newly developed blood vessels also provide a pathway for the tumour cells to enter the blood and lymphatic vessels . Like normal epithelial tissue cells, there are multiple tight cell connections betweenBCcancercells,whichisnotconducivetocellmovementandinvasion. Thus,theBC cells need to lose some epithelial phenotype by going through epithelial-to-mesenchymal transition (EMT) . Then, at the primary tumour site, the BC cells induce the secretion of amajorclassofmatrixmetalloproteinase(MMPs)essentialfortumourcellinvasion. Under the action of MMPs, the tumour cells break through the basement membrane and enter the extracellular matrix and surrounding normal tissues [7].

Migration:

Aftertheinvasion, thetumourcellsenterthebloodcirculationandbecomecirculating tumour cells (CTCs), disseminating to the bone via blood vessels or lymphatic vessels. The CTCs may travel as single cells or as multicellular clumps. These clumps can persist in the circulation system until encountering small-calibre capillaries. Most of the CTCs may be cleared immediately. However, clusters of CTCs can move through microvessels by holding together their adhesive interactions to form a single-cell chain [8].

Finally, the CTCs arrive at the bone and enter the parenchymal tissue by degrading the vascular basement membrane and penetrating the blood vessel. In the bone microenvironment, the CTCs eventually become disseminated tumour cells (DTCs). To adjust the bone microenvironment, DTCs change their biological phenotype. For example, DTCs can avoid destruction and last a long time in the tissue parenchyma. Additionally, DTCs may survive by their capability of withstanding anoikis, for instance, through expressing the tyrosine kinase receptor TrkB or through non-canonical WNT signalling [9].

Adhesion:

DTCs adhere to the favourable metastatic microenvironment, usually bone marrow for bone metastasis . This step is mainly mediated by integrin and cadherin. Integrin is an isodiglycan protein that belongs to a heterodimeric transmembrane glycoprotein family. Integrins can mediate the BC cells' adhesion to the extracellular matrix. Among the whole family, the αvβ3 integrin plays a vital role in regulating the migration of BC cells to the trabecular bone by binding to at ripeptide(Arg-Gly-Asp) present in vitro nectin, osteosialin, and osteopontin [10].

E-cadherin is an epithelial-specific transmembrane glycoprotein mediating cell-cell adhesion, maintaining normal cells' cellular polarity and epithelial morphology. This glycoprotein plays an essential role in maintaining epithelial phenotype, and the loss of E-cadherin may give tumour cells the properties of migration and invasiveness. Furthermore, E-cadherin and N-cadherin mediate the interaction between BC cells and bone marrow stromal cells, promoting the homing progress of BC cells. Cadherin-11 has been proven to be overexpressed in various favourable metastatic sites for BC, such as brain, lung, and importantly, bone. The migrative and invasive capability of BC cells will be reduced when cadherin-11 is inhibited, indicating the vital role it plays in the process of BC bone metastasis [11].

Survival:

After adhesion to the bone tissue, the proliferation of BC cells in the bone is the last but vital step of metastasis. The survival of tumour cells relies on the "vicious cycle of bone metastasis" . In the bone micro-environment, BC cells firstly overexpress parathyroid hormone-related protein (PTHrP), which subsequently stimulates the expression of RANKL and suppresses the expression of OPG . When the balance between OPG and RANKL is broken, the function of osteoclasts is promoted, which results in bone resorption. During this process, the release of growth factors, such as transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factors(IGFs),BMPs,andcalcium,isongoinginthebone microenvironment. Itwasproven that the increase in intracellular calcium levels among BC cells could interfere with the osteogenic function and facilitate survival [12].

Conventional Treatments of BC Bone Metastasis:

The main therapeutic aims of metastatic BC treatment are to prolong life and relieve symptoms . In the past few decades, the primary therapeutic methods for BC bone metastasis have been divided into systematic and local treatments. The former includes systemic administration of anti-resorptive, antitumour compounds, and radiopharmaceuticals, while the latter includes surgery and radiation therapy. The key challenge is that most antitumour agents are cytotoxic, leading to severe nephrotoxicity, hepatotoxicity, and adverse effects on other normal organs if not selectively delivered to metastatic lesions. Moreover, the administration of anti-resorptive compounds may exert negative impacts on healthy bone tissue. Although local palliative treatments could help extend the patients' overall lifespan, they cannot significantly improve the survival rate. Furthermore, the severe side effects during the treatment seriously impact the patients' quality of life [13].

Targeting Agents for BC Bone Metastasis:

In targeted DDSs, the targeting agents play vital roles. The drug can be accurately delivered to the metastatic tumour sites with targeting agents, increasing the treatment efficacy and decreasing side effects generated by some cytotoxic compounds. Various bone targeting agents include tetracycline, bisphosphonate, γ-carboxylated glutamic acids (Gla) and some aminoacids (e.g., asparticacid (Asp), and glutamic acid (Glu)), and aptamers are investigated in different cancers . However, the most commonly used bone targeting agents for DDS shave involved Arginine-Glycine-Aspartic acid (RGD)peptide, and two drugs from bisphosphonates family, alendronate and zoledronic acid [14].

Arginine-Glycine-Aspartic Acid (RGD) Peptide and Its Derivative:

Integrins are a group of divalent cation-dependent heterodimeric membrane glycoproteins composed of α and β subunits, playing vital roles in cell-cell and cell-extracellular matrix (ECM) adhesion . Among all subtypes of integrins, overexpression of αvβ3 integrin

has been proven to be related to BC bone metastasis and poor prognosis and decreased survival time of BC patients . As an integrin predominantly expressed in blood vessels, αvβ3 integrin can mediate angiogenesis, cell proliferation, and metastasis in several types of cancers. If αvβ3 integrin is blocked with integrin antagonists, angiogenesis of some tumour cells, such as melanoma, prostate cancer, and BC cells, would be disrupted . Furthermore, by binding to fibronectin, fibrinogen, or osteopontin, αvβ3 integrin induces the migration of endothelial cells, and it activates several signalling cascades, which protect the cells from apoptosis [15].

Bisphosphonate:

Bisphosphonates (BPs) are a group of chemical compounds showing high affinity to hydroxyapatite (HA) crystals commonly seen in bones and teeth. The reason for this high affinity is that BPs can generate bidentate or tridentate chelation with the calcium ion on the HA . The BPs can recognise and localise quickly to tissues where HA is present after intravenous or oral administration. Thus, conjugation of BPs to the DDSs provides a promising strategy to target specifically to the bone . Furthermore, BPs are widely used in the treatment of conditions where bone resorption occurs. BPs can be selectively taken up by osteoclasts. By inactivating osteoclasts, they can simultaneously exert specific auxiliary therapeutic effects on SREs, such as increasing bone density, decreasing fracture risk, and relieving bone pain at the metastatic sites while playing the targeting role . Different BPs can be distinguished by side-chain groups at R1 and R2 sites[16].

Alendronate:

Alendronate, a second-generation BP, has been used as a bone-targeting agent in treating metastatic lung cancer , breast cancer, primary bone cancer, and metastatic bone cancer. More importantly, a study by Rouach et al. showed that in early breast cancer in postmenopausal patients, a previous history of oral alendronate consumption is linked with a lower likelihood of bone metastases. In addition, alendronate has been extensively used for functionalizing nanoparticles to achieve various targeted delivery to the bone.

Zoledronic Acid:

Zoledronic acid, a third-generation BP, has been proven to be a cost-effective solution in treating bone resorptive diseases, such as osteoporosis and osteoporotic fractures . The administration of zoledronic acid could significantly reduce the pain and improve the quality of life among BC patients with bone metastasis in the clinic, suggesting an additive therapeutic effect. Due to a high affinity to bone, zoledronic acid has strong targeting potency and can be employed as a targeting agent in DDSs to treat BC bone metastasis [17].

Advanced Targeted DDSs:

Nanoparticles have been under investigation for a few decades because of their capability to alter the drug's pharmacokinetics. The introduction of nanoparticles can solve the poor solubility of some hydrophobic drugs and reduce the metabolism, thus preventing the drug compounds from being degraded in the microenvironment. The utilization of nanoparticles for effective delivery of active pharmaceuticals could also promote the enhanced permeability and retention effect (EPR), which is widely observed in the vasculature of tissues undergoing pathologies. Notably, only nanoparticles whose sizes are no more than 200 nm have the property of easily penetrating through mucus without being removed by the natural size-filtering mechanism. The surface of the nanoparticles can be modified as needed to achieve specific requirements of different disease conditions [18].

Targeted DDSs Loaded with Anticancer Agents:

Cisplatin Prodrug To deliver cisplatin prodrug (DSP) to B C bone metastatic lesions, Heandco-workersdevelopedZn2+ coordinationpolymerparticlescoatedwithalendronate-conjugatedpolyethylene glycol (PEG). The nanoparticle (DSP-Zn @ PEG-ALN NP) had an average size of about 55 nm, which endowed the nanoparticles the ability to penetrate the slits (80 nm) of the bone sinusoidal capillaries and successfully transfer to the metastasis. Results from the in vitro HA binding test suggested that targeted DSP-Zn @ PEG - ALN NPs had higher binding potency to the bone than non-targeted nanoparticles and free cisplatin [19].

Bortezomib:

Bortezomib is a protease inhibitor widely investigated in treating various cancers, such as myeloma, prostate, and lung cancers. Wang and co-workers developed atripeptide RGD-targeted dendrimer for the delivery of bortezomib to metastatic tumour sites. With a boronate-catechol linkage, the dendrimer was endowed with pH-responsive properties. The result from in vitro targeting assay indicated that the conjugation of RGD could successfully lead the dendrimers to the MDA-MB-231 cells. Besides, the X-ray and micro-CT results showed that the bone destruction of the tibias in the RGD-targeted nanoparticle treated group was the lowest while the bone volume and trabecular

number were the highest compared to the control groups. These results suggested that the RGD-targeted dendrimer could suppress the osteolysis caused by BC cells.

Curcumin:

Redox-sensitive alendronate targeting micelles loaded with curcumin (ALN-oHA-SS-CUR) was formulated by conjugating the hydrophobic curcumin (a naturally derived compound) to hydrophilic oligosaccharides hyaluronan (oHA) via disulphide bonds. oHA is a hydrophilic polysaccharide that can selectively bind to the CD44 receptor, which is overexpressed in different tumour cells. In vitro, ALN-oHA-S-S-CUR showed higher uptake and cytotoxicity in MDA-MB-231 cells than in MCF-7 cells because the latter cell line has a lower expression of CD44 receptor. In a spheroid model mimicking the tumour in vivo, ALN-oHA-S-S-CUR showed a deeper penetration in the multicellular 3D MDAMB-231 cell spheroid than in the non-targeted group. The researchers subsequently tested ALN-oHA-S-S-CUR in vivo, and it showed high binding affinity, robust antitumor, and anti-resorption activity in MDA-MB-231-burdened mice [20].

Bortezomib and Curcumin:

Alendronate-targeted nanoparticles composed of poly (D, L-lactide-co-glycolic) acid (PLGA)loadedwithcurcuminandbortezomibweredesignedbyThamakeandco-workers. In vitro bone targeting studies indicated that these targeted nanoparticles had increased affinity to the bone tissues. Furthermore, the alendronate conjugated nanoparticles could localise at a significantly higher rate and quantities with a more prolonged accumulation at the tumour site than the control groups in a bone metastasis model induced by intratibia injection of MDA-MB-231 model in vivo. Furthermore, the targeted nanoparticles could inhibit the process of bone resorption and tumour growth in vivo. However, the combination of curcumin and bortezomib did not exert any synergistic effect in the antiosteoclastogenic activities in the bone [21].

Doxorubicin:

Zhao and co-workers designed a pH, and redox dual sensitive core crosslinked nanoparticle (DOX@ALN-(HA-PASP) CL) loaded with doxorubicin. These nanoparticles erebased on hyaluronic acid (HA)forspecificbindingtoCD44receptorsexpressedin BC cancer cells, and poly (aspartic acid) (PASP) DOX@ALN-(HA-PASP) CL showed enhanced bone affinity compared to the non-targeted nanoparticles in in vitro and in vivo assays. In an anti-bone resorption study in in vitro 3D model of breast cancer bone metastasis, the numberofbonelacunasandosteoclastsinducedbyMDA-MB-231cellsatthecalvarialsites were significantly decreased in DOX@ALN-(HA-PASP) CL -treated groups compared to the control groups, which indicated the anti-bone resorption ability of these two nanoparticles. Among MDA-MB-231 bearing mice, the administration of DOX@ALN-(HA-PASP) CL could represstumourgrowthandsignificantlyincreasetheratio ofbonevolumetotissuevolume, which is an indicator of less bone resorption. Pham et al. fabricated a doxorubicin-loaded, alendronate-modified DDS based on PLGA, which showed significant bone targeting, antitumor and anti-bone resorption [22].

Docetaxel:

An alendronate-functionalized amphiphilic triblock micelle based on PEG, polyglutamic acid, and polyphenylalanine (PEG-PGlu-PPhA) (ALN-m/DTX) was prepared to deliver docetaxel to metastatic sites of BC. In in vitro studies, ALN-m/DTX could exert a potent cytotoxic effect in a 4T1 cell model that was mimicking the bone microenvironment with hypercalcemia. Those micelles also showed an improved capability for binding to the bone and inhibiting the progress of osteoclast genesis, bone resorption, and tumour induced macrophage migration both in vitro and in vivo. In addition, the development of bone metastasis was delayed, and the weight loss was significantly controlled after the administration of ALN-m/DTX in a mouse BC bone metastasis model induced by injecting 4T1 cells into the left cardiac ventricle of female BALC/c mice . Another amphophilic phospholipid polymer functionalised with alendronate (PMBADTX) was developed to carry docetaxel. The targeted nanoparticles showed antitumour activity among various BC cell lines (MDA-MB-231. MCF-7 and 4T1) in vitro and an enhanced accumulationat bone tissue in vivo [23].

Paclitaxel:

APLGA-based DD Swith two targeting agents was designed, alendronate(A) forbone targeting and folic acid (FA) for targeting cancer cells that overexpress the folate receptors. Paclitaxel was loaded in the hydrophobic pocket of D-α-tocopheryl polyethylene glycol succinate (TPGS), and different targeted NPs were fabricated. Considering the HA binding test results, in vitro cellular up-taking test, and in vitro cytotoxicity test, the PTX-AFTPNs (A to F ratio: 0.67) showed the best dual-targeting potency and was further studied in vivo. Although both mono(A) and dual (AF) targeted NPs,i.e., ATPNs and AFTPNs(A:F=0.67), were localised in bone lesions

more than the control groups, mono-targeting nanoparticles (ATPNs) exhibited higher affinity to the bone than AFTPNs (A:F = 0.67). This effect was probably due to the presence of FA that decreases the percentage of alendronate on the surface of nanoparticles. PTX-AFTPNs showed the highest antitumour activity at the metastatic bone sites of 4T1 tumour-bearing mice, the best survival rate and an improved bone morphological integrity.

Non-Cytotoxic Payloads Apart from the tr additional anticancer compounds, alendronate-functionalisednanoparticlescouldalsobeaneffectivecarrierforspecificinhibitorsoftranscriptionfactors. Asmall molecular inhibitor of transcription factor Gli2 (an upregulator of PTHrP), GANT58, was encapsulated in alendronate-conjugated amphiphilic diblock copolymer-based nanoparticles (GANT58-BTNPs). It was reported that 10% of alendronate (based on molar ratios) in the hydrophilic polymer block gave rise to the best balance between systemic pharmacokinetics and bone affinity. This amount of alendronate resulted in the highest bone to live biodistribution ratio. The administration ofGANT58-BTNPscouldsignificantlyinhibit tumorigenesis and bone resorption in a mouse intracardiac model of bone metastasis. The bone volume fraction in the tibiae of the GANT58-BTNPs treated group was significantly higher than drug-free alendronate-conjugated nanoparticles, indicating that alendronate and GANT58 could exert dual beneficial therapeutic effects [25].

Targeted DDSs with Immunostimulatory Payloads:

Bisphosphonatessuchaszoledronicacidhavealsobeenusedfortheselectivedelivery of immunostimulatory agents. Pang and co-worker designed zoledronic acid-modified bone targeting metal-organic framework (MOF) nanoparticles loaded with immunostimulatory cytosine-phosphate-guanosine (CpG) (BT-isMOF). Both results from in vitro and in vivo studies indicated that BT-isMOF nanoparticles had a robust capability of targeting the metastatic bone lesions, leading to a significant reduction in the osteoclast-mediated bone resorption and simultaneous induction of macrophage polarisation to the M1 pro pro-inflammatory cytokines, which may also play a role in the antitumour activities [26].

Targeted DDSs Loaded with Contrast Agents:

Bisphosphonate-conjugated nanoparticles loaded with contrast agents could play a role in diagnosing BC bone metastasis. Qiao et al. developed zoledronic acid-conjugated gadolinium (III) upconversion nanoparticles (PUCZP) by encapsulating plumbagin and poly (acrylic acid) (PAA) inside bimodal mesoporous silica. With the existence of gadolinium (III), a contrast agent in T1-MRI, PUCZP could help to detect early bone metastasis, which is generally hard to diagnose by standard radiography. With the help of PAA, the nanoparticles could release in a pH-sensitive mode in the osteoclast acidity (pH = 4.5~5.5). Furthermore, PUCZP could inhibit the expression of RANKL and further suppress the osteocyte-induced osteoclast formation and weaken the invasive properties of MDA-MB231 and 4T1 cells in vitro. In addition, UPCZP could repress tumour growth and osteoclastogenesis in a mouse intracardiac model of BC bone metastasis.

Targeted DDSs Loaded with Photothermal Therapeutic Agents:

Photothermal therapy (PTT) is a method that converts absorbed photon energy to heat by utilising photo-absorbing materials and killing the cancer cells under a near-infrared (NIR) laser. According to relevant studies, PTT is capable of antitumour activity by itself and could increase the sensitivity of tumour cells to anticancer compounds, which further improves the efficacy of chemotherapy. In addition, PTT shows favourably noninvasive and controllable features. If combining the antitumour drugs with photothermal agents, the NIR laser could be regarded as a trigger to promote the release of the loaded drugs.

Zoledronicacidiswidelyemployedinthosenanoparticlesdesignedascarriers for photothermal agents[27].

CONCLUSION:

Targeted cancer therapies are medications or other substances that stop cancer from growing and spreading by interfering with specific molecules (called "molecular targets") involved in cancer's growth, progression, and spread. "Molecularly targeted pharmaceuticals," "molecularly targeted therapies," "precision medicines," and other terms are used to describe targeted cancer therapy.

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