Application of Nanomedical Technology in Breast Cancer Treatment

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SUMMARY

Introduction: Despite the progress in breast cancer treatment, currently used methods are often aggressive and with low selectivity, thus inducing systemic toxicity while obtaining limited effect. The application of nanotechnologies is a promising novel technology, which could overcome these limitations.

Corresponding section headings: Incorporation of the medication into a nanocarrier enables the administration of molecules with the suboptimal pharmacokinetic profiles if given as free agents. Furthermore, nanomedicine could improve the safety profile of currently used chemotherapeutics, by modifying pharmacokinetic properties and prolonging the half-life of the therapeutic. Most importantly, it provides a possibility of designing drug carriers with selective delivery to malignant cells, based on their characteristics.

Conclusion: This advantage initiated an entirely new subset of targeted breast cancer therapy development, and has demonstrated favorable outcomes even in treatment of aggressive malignant types, metastatic developments, and multi-drug resistance.

Keywords: breast cancer, nanomedicine, molecular targeted therapy, nanoparticles, drug carriers

INTRODUCTION

Malignant breast neoplasm is the most frequently diagnosed malignancy in women, representing the second leading cause of all cancer-related deaths [1,2]. As a result of continuous research and implementation of new therapeutic and diagnostic options five-year survival of women breast cancer patients increased from 75% (1975-1977) to 90% (2005-2011) [3]. However, current strategies still largely rely on chemotherapy and other non-specific approaches [3]. Cytotoxic nonspecific therapies do not provide successful tumor eradication since it is difficult to achieve high concentrations in the neoplastic cells due to a narrow therapeutic window of the drug. Thus, concentrations are similar between malignant and normal tissue, resulting in substantial systemic toxicity. Toxic adverse effects strongly affect patients' health, quality of life as well as patients' compliance [4,5]. In addition, if the malignant cells are not effectively eradicated, there is a considerable tendency for chemo-

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therapeutic resistance development [6]. If the malignant neoplasms establish resistance patterns, the treatment becomes much more challenging, greatly reducing the likelihood of favorable outcome [7]. Furthermore, advanced stages of breast cancer, particularly the metastatic phases are difficult to confront with use of conventional approaches, thus represent the prevailing cause of mortality [7]. An emerging area that shows high potential in overcoming these obstacles is the development of nanotherapeutics. Countless possibilities of nanocarrier structural alterations provide them with various characteristics and functions to satisfy versatile patient-specific medical needs.

CORRESPONDING SECTION HEADINGS

Breast malignancies

Breast cancer alone accounts for 30% of all newly diagnosed malignancies in women in the United States, with an estimated incidence of 63 000 patients with *in situ* tumors and a total number of 271 000 newly diagnosed patients in 2019 [1]. In the last decade, the incidence is moderately increasing, partially due to the rising obesity epidemic [1,8]. Patients diagnosed in the early phases of the disease have promising chances for successful therapy. Nonetheless, metastases will eventually occur in almost every third patient firstly diagnosed with *in situ* cancer [9]. When the disease is diagnosed at advanced stages, therapeutic options are limited and five-year survival decreases to only 26%. The most frequent mortality cause is metastatic dissemination in lymph nodes, bones, liver, lung and CNS [9].

Treatment approaches

The strategy for breast cancer treatment is most commonly multimodal and includes combinations of local treatments such as surgical methods and/or radiotherapy, and systemic therapy that comprises of chemotherapy, hormonal and targeted therapy [3]. The proper choice of therapy highly depends on the stage of the disease and the molecular type of cancer cells. Accordingly, local therapy has better outcomes in the treatment of early stages malignancies, whereas later stages, especially if metastases occur, require the addition of systemic therapy as the efficacy of radiotherapy

and surgical procedures are attenuated [2]. In addition, the determination of tumor molecular type is crucial for proper therapy choice. Survival of cancer cells is usually dependent on the specific molecule that is driving the oncogenic process and its inhibition results in cellular death. Thus, these specific molecules can serve as targets for both differentiation between the normal and malignant cells and for successful induction of cancer cell apoptosis. Therefore, determining the molecular basis of breast cancer by immunohistochemistry and other molecular biology methods enables the prediction of the pharmacological agent that the cancer cells will respond to [3,9].

Molecular types of breast cancer

Depending on the expression of hormone receptors for estrogen (ER) and progesterone (PR), and human epidermal growth factor receptor 2 (ERBB2, also known as HER2), breast cancers are classified into: hormone receptor positive (70% of patients), ERBB2 positive (15-20%) and triple-negative tumors which do not express any of the three molecular markers (15-20%) [9]. In accordance, hormone receptors positive and HER2 overexpressing breast cancers can be effectively treated with appropriate selective inhibitors such as small molecules and monoclonal antibodies. In addition to the most commonly used antibodies for HER2 inhibition such as trastuzumab and pertuzumab, they can be treated with both HER2/neu and epidermal growth factor receptor (EGFR) inhibitors lapatinib and neratinib [10]. However, basal or triple-negative breast cancer (TNBC) cells do not express any of the receptors that could currently be effectively targeted, therefore presenting the most challenging type to treat. Despite the relatively low prevalence, this is the most aggressive type which in addition lacks targeted therapeutic options, therefore having the highest mortality rates [7]. The standard therapeutic approach includes nonspecific chemotherapy which largely includes taxanes, anthracyclines and cyclophosphamide [11]. Even if the treatment is curative, the risk of relapse is higher than in other molecular types, and TNBC has a high tendency for metastatic dissemination. Therefore, this is the molecular type of breast cancer with the greatest necessity for the development of new therapeutic methods.

Despite the targeting properties and

specificity of some of the therapeutic strategies, other pharmaceutics are defined by low specificity with consequent modest effectiveness along with systemic toxicity which damage healthy tissue [12]. Moreover, even when targeted options are appropriate, they are commonly combined with a nonspecific agent. In addition, some agents can have undesirable pharmacokinetic (PK) profile defined by suboptimal absorption and permeability through biological membranes, short circulation half-life, and low bioavailability, insufficient biodistribution in the target tissue and nonspecific effects with notable toxicity on healthy tissue [13]. Novel researches are directed towards overcoming these limitations and one of novel promising tool is the development of nanomedicine. Nanomedicine has the potential of overcoming some, if not all the listed constraints [14,15].

Nanomedicine

Nanomedicine represents a novel compelling form of pharmacotherapy in the treatment of numerous common diseases such as diabetes, cardiovascular diseases, infective diseases as well as various types of malignancies, including breast cancers [14-17]. It is defined as a biomedical application of materials with at least one dimension below 100 nm [18]. Incorporation of a therapeutic agent into a nanoscale carrier enables *in vivo* administration of various molecules which would be otherwise impossible due to extremely poor PK profile, such as for siRNA, miRNA, genes, peptides, etc [19]. As for the cytotoxic agents that have modest but applicable PK features, they are protecting the active substance from degradation in circulation and enabling its controlled release, eminently affecting drug stability [20]. As a result, drugs do not exert very high blood concentrations and elimination half-life is prolonged [21]. For instance, Ran et al. showed that the maximum tolerated dose of a chemotherapeutic drug mertansine, clinically used for TNBC treatment, is 8-fold increased when incorporated into a nanocarrier [22]. Furthermore, nanoencapsulation enhances endo- and transcytosis of otherwise poorly permeable substances, resulting in augmented intracellular concentration [23,24]. Importantly, nanotherapeutic surface alterations provide the opportunity of preferentially delivering chemotherapy agents to malignant cells based on the differential expression of molecules on the plasma membrane [25]. As a consequence, higher concentrations are obtained at the target site, while minimizing the uptake in healthy tissue and reducing overall toxicity [25,26].

Nanomedicine is excessively investigated as a tool in breast cancer treatment, with currently 75 ongoing clinical trials testing new nanoscale formulations [27] and even greater numbers in the preclinical stage. So far, several formulations gained approval by the US Food and Drug Administration (FDA), most of which are indicated in oncology. Three of the liposomal formulations, Doxil®, Abraxane® and MyoCet® are already widely used in the treatment of breast cancer.

Nanomedicine

Liposomes

Liposomes are spherical particles with a hydrophilic core and a membranous lipid bilayer surface. Hydrophilic drugs, genes or RNA-inhibiting molecules siRNA and miRNA can be encapsulated in their inner hydrophilic portion [19]. On the other hand, lipophilic drugs can be loaded in the lipid bilayer, thus extending circulation half-life with following reduction of systemic toxicity. In addition, coating with inert biocompatible polymers such as polyethylene glycol (PEG), reduces the recognition by the reticuloendothelial system, and elimination [26]. Doxyl®, the PEGylated doxorubicin liposome is widely used in breast cancer treatment for the listed benefits over a free drug. The limitations of liposomes mainly result from physiochemical instability, along with the ability to load only a certain number of lipophilic drugs, such as paclitaxel, into the single lipid bilayer [12].

Nanoparticles

Polymeric nanoparticles, such as micelles, capsules, colloids, and dendrimers, have been developed in parallel with the growing need for nanoscale carriers of greater capacity for hydrophobic substances including taxanes, cisplatin, and tamoxifen. They consist of a hydrophilic shell and a lipophilic core, with the addition of amphiphilic molecules, polymers, and copolymers with PEG to prevent agglomeration [13]. Hydrophilic agents may be bound to the

outer layer by covalent or hydrogen bonds, thus reducing the immunogenicity of certain anticancer drugs such as the ones of protein source [12]. In addition, alternatingly charged multilayered nanoparticles have a considerably higher capacity for molecule loading, and can accept external molecules up to 50% of the nanoparticle weight [28]. Another benefit of these systems is the controlled drug release in response to certain factors such as pH, UV or temperature [29]. Lipid nanoparticles are similar, designed for loading the molecules of same affinity, yet stabilized and solubilized by surfactants and emulsifiers [30].

Carbon nanoparticles include carbon nanotubes and fullerenes depending on their structural organization into a tube or hollow cage shape. Carbon nanotubes are largely studied for their mechanical properties as tools in radiation oncology, biomedical imaging, as quantum dots and biosensors [31]. However, uncertainty regarding toxicity aspects of their administration remains to be revealed [31]. On the other hand, fullerenol derived nanoparticles are distinguished for their reactive radicals scavenging ability and anti-oxidative effect, while retaining a safe genotoxicity profile [32-34]. Utilizing this feature might contribute to the safety aspects of certain chemotherapeutic agents in breast cancer treatment [35]. For instance, doxorubicin-induced oxidative stress may lead to cellular membrane lipid peroxidation in the heart, bone marrow, gastrointestinal tract, and other tissue, resulting in pronounced systemic toxicity and increased risk of congestive heart failure [36]. Coupling with an antioxidant carbon nanoparticle such as fullerenol $C_{60}(OH)_{24}$ could ensure a safer doxorubicin profile, as proposed by in vivo studies [37,38]. In addition, several studies revealed fullerenol particles themselves to exert potent anti-tumor and anti-metastatic activity in murine breast cancer models [39,40].

Metal nanoparticles, including gold and silver nanoparticles are used to deliver a sensitizing agent during radiotherapy or as contrast enhancers, in addition to previously described features of nano-systems [41]. Compellingly, they can possess a peculiar ability to absorb near-infrared rays and emit absorbed energy in the form of heat during the process of photothermal ablation (PTA) [42]. The temperature of the surrounding tissue then increases to 50°C inducing irreversible cellular damage, resulting in complete breast tumor cells removal *in vivo* [43]. Similarly, certain polymeric nanoparticles, such as lipid-PEG layer coated polylactic-coglycolic acid (PLGA), are light-absorbing photosensitizers that generate reactive oxygen species when illuminated, therefore resulting in damage of the nearby tissue during the process of photodynamic therapy [44]. The external layer of these and previously described particles can be conjugated with a tumor-targeting molecule, thereby inducing selective damage to tumor cells [43]. This approach showed promising outcomes in breast cancer treatment and may represent a suitable non-invasive alternative for patients whose chemotherapy or radiation treatment did not produce any beneficial effect.

Passive targeting of breast cancer using nanotherapy

The targeted effect on malignant cells using nanomedicine formulations can be active or passive. Retention of nanoforms in vascular tumor tissue is a common example of passive targeting. Breast cancers and other solid tumors develop their own vascularization which differs from the normal blood vessels, inter alia, by having greater permeability [45]. Therefore, the leaky vasculature makes the tumor tissue highly accessible to nanoscale molecules [46]. Additionally, lymphatic drainage is reduced allowing prolonged retention in tumor tissue [47]. Although this mechanism is quite simple and nonspecific, it provides significantly higher nanoparticle concentrations at the tumor site, known as the enhanced permeability and retention effect (EPR)[48]. Abraxane®, the FDA approved liposomal paclitaxel is a typical example of efficient passive targeting of breast cancer cells. This effect strictly depends on the abnormal tumor vessel development which occurs in the initial phase of tumorogenesis, however early lymphogenic metastasis will hardly be targeted using this strategy [49]. Another method for nonspecific targeting is based on the hypoxic microenvironment of breast cancers and other solid tumors, resulting from insufficient tumor vascularization. Hypoxic microenvironment might further facilitate the development of somatic mutations and therefore contribute to cancer progression and metastatic behavior. Furthermore, the hypoxic setting might promote resistance to various anti-cancer drugs, at least partially

by means of poor vascularization that results in insufficient drug accumulation [6,50]. Low oxygen state of tumors facilitates anaerobe cellular metabolism resulting in acidic pH of the surrounding tissue. Nanotherapeutics can be constructed to have greater affinity and/or to be cleaved at lower pH conditions, thus releasing the drug, while having improved stability in the range of physiological pH [51-53].

Active targeting of breast cancer using nanocarriers

Active targeting implies complementing the surface layer of the nanocarrier with a molecule that has a specific affinity to bind the structures aberrantly expressed on the surface of malignant cells. This type of targeted therapy is more advanced than passive targeting, as it can achieve greater specificity and more effective selectiveness of drug delivery, followed by greater accumulation at the tumor site. Typical molecular structures that can be used to supplement the nanocarrier surface are monoclonal antibodies and ligands of the targeted receptors. For instance, CD44 cell surface adhesion receptor is highly expressed in a variety of malignant diseases, including breast cancer stem cells, thus nanocarriers complemented with its ligand, hyaluronic acid, exert tumor-targeting properties [54,55]. Similarly, in targeting HER2 positive breast cancers, nanoparticles can be terminally complemented with trastuzumab [56]. Although antibody-covered nanoparticles express precise selectivity and can be very effective, it is possible for large antibody structure to alter the physiochemical properties of the nanoparticle, modifying their PK profile. Therefore, researchers are also investigating the complementation of nanoparticles with peptides as targeting agents [57,58]. The potential of nanomedicine in the treatment of breast cancer is particularly important in TNBC, which currently lacks targeted therapeutic options. Since almost half of the TNBC has elevated EGFR expression, an appealing strategy for selective TNBC treatment is drug nanocarriers coated with anti-EGFR peptides and antibodies [59-61]. Additionally, folate receptor alpha (FRα) represents a promising target for selective TNBC treatment as it is expressed in 50-85% of metastatic TNBC [62-64]. In a nonmalignant manner, FRα tissue distribution is limited to a certain number of epithelial cells, with expression localized at the apical tissue margins hardly reachable by blood circulation [65]. Furthermore, oncogenic transcription factor signal transducer and activator of transcription 3 (STAT3) is abnormally activated in a variety of malignant diseases including 70% of breast cancers and almost all TNBC cases and might serve as a potential target for designing selective therapy for this aggressive neoplastic disorder[66,67].

Nanotherapy in drug resistance prevention and management

Resistance to anti-cancer medications represents one of the most challenging obstacles in the treatment of breast cancer. Resistance patterns might evolve through various mechanisms, such as modification of the receptor that is responsible for the drug uptake, mutation of the gene that encodes the drug-binding protein, enhancement of cellular efflux etc [6]. Some of these issues might be solved using passive targeting nanocarriers, by ensuring higher drug concentration in tumor tissue and not permitting tumors enough time to develop the resistance mechanisms [68]. Another attractive method for resistance prevention and management is the application of combination therapy in a single nanoparticle. Thus, antitumor agents can be administered together with the inhibitor of the signal pathway responsible for resistance development, even if they are otherwise incompatible or either of them shows insufficient PK properties without an appropriate carrier. In the past decade the research was extensively focused on combining cytotoxic agents with RNA interfering molecules, siRNA and miRNA [69]. However, extremely low stability in circulation and inability to cross the plasma membrane disputes their use as free agents. With the employment of nanocarriers, treatment can be combined with siRNA to resistance-responsible gene [70] or as drug-sensitizing agents [71,72]. Moreover, all the components of combination therapy would be absorbed by the targeted cell at the same moment, enabling efficient synergistic effect and preventing resistance development [73]. Aside from additive agents, RNA interference is tested as single nanoparticle-conjugated therapy for the treatment of various malignancies [74]. For instance, Asik et al. successfully suppressed the growth of BRCA1-mutated breast cancer using nanoparticles loaded with eukaryotic elongation factor 2 ki-

nase (EF2K) siRNA *in vivo*, as its expression is upregulated in almost 80% of patients with this genetic alteration [75].

Nanoparticles in treatment of breast cancer metastases

In addition to previously described methods for targeted drug delivery, various strategies have been investigated for the treatment of certain metastatic malignancies. Ross et al. have shown in a mouse model of metastatic breast cancer that it is possible to deliver chemotherapy specifically to breast cancer bone metastasis, as they have changed their primary characteristics in response to specific bone micro environment [76]. They found integrin β3 to be differentially expressed in bone metastases and have therefore designed docetaxel-loaded nanocarriers conjugated with integrin β3 targeting agent. Hence, drug delivery to healthy tissue is reduced, which was verified by unaltered markers of liver, renal, blood cells and other vital functions. In an opposite manner, free docetaxel treatment showed systemic toxicity in mice [76]. The different study used a combination of two targeting molecules directed towards αvβ3 integrin and P-selectin, as they are expressed in different stages of breast cancer metastasis. As these nanoparticles are targeting different metastatic sites that overexpress either or both of the receptors, they have observed the accumulation of injected particles at 89% of the confirmed metastatic sites [77]. Similarly, separate study efficiently targeted breast cancer lung metastases using nanoparticles coated with integrin-binding exosomes for their navigation to tumor sites [78]. Breast cancer metastases in CNS are one of the most challenging to treat due to their localization and aggressiveness. The effectiveness of chemotherapy is usually suboptimal, as most of them have low permeability through hematoencephalic barrier. To address this complication, nanoparticles can be supplemented with polysorbate 80 (PS80) as it enhances the hematoencephalic barrier penetration resulting in more effective brain tumor burden reduction, as demonstrated in mice [79].

Currently available forms of nanomedicine indicated in breast cancer therapy

Doxil® (Johnson & Johnson) in the USA or Caelyx® (Janssen-Cilag International NV) in Europe was the first nano drug indicated for breast cancer treatment, which was approved by the FDA in 1995. It is a PEGylated liposomal formulation of doxorubicin with a diameter of approximately 85 nm. Doxorubicin has been an essential element of breast cancer treatment for decades. However, its systemic toxicity and cardiotoxicity in particular, significantly limit the extent of its clinical appliance [36]. Therefore, incorporation of doxorubicin in PEGylated formulation reduces premature drug release, consequently attenuating systemic toxicity without affecting the antitumor effect. Thus, with this type of formulation, the incidence of cardiotoxic side effects is decreased five-fold. Furthermore, the circulating half-life of Doxil® is approximately 74 hours, whereas it is approximately 5 minutes for free doxorubicin, at the starting dose of 60 mg/kg [80].

MyoCet® (GP-Pharm) is the second, however non-PEGylated liposomal form of doxorubicin approved for metastatic breast cancer treatment by FDA in 2000, although currently licensed only in Europe and Canada [36]. It has certain advantages over free drug application, yet its clearance rates are significantly higher comparing to its PEGylated analog Doxil® [81].

Abraxane® (Celgene Corporation) is a nanotherapeutic with albumin-bound paclitaxel, the so-called nab-paclitaxel. Like other taxanes, paclitaxel exerts its action by binding to microtubules, polymerizing tubulin and stabilizing tubular polymers, thus inhibiting their degradation during cell division, resulting in mitosis arrest. The clinical success of paclitaxel is confined by its low solubility in aqueous media. This limitation is solved by non-covalent bound to human serum albumin, the physiological carrier of circulating lipophilic components [82]. In addition, albumin has a binding affinity for the vascular endothelial membrane protein Gp60, which in turn increases vascular membrane permeability and receptor-mediated uptake of circulating proteins into the interstitium. Therefore, intratumoral tissue concentration of nab-paclitaxel is 33%, higher in comparison with free drug administration, resulting in a higher frequency of pathological complete response in breast cancer patients [83,84]. Abraxane® was approved by the FDA in 2005 and is currently widely used for the treatment of metastatic

breast cancer and if cancer has relapsed within 6 months of chemotherapy. Additionally, its effects are investigated for neoadjuvant therapy and in the treatment of early stages of breast malignancies [85-87]. Innovative approaches are directed towards enhancing the activity of nab-paclitaxel, such as by conjugation with manganese dioxide which induces the oxygenation of hypoxic tumors, resulting in two-fold more effective tumor growth inhibition [88]. Certainly, as in other nanotherapeutic types, complementation with antibodies such as trastuzumab, bevacizumab or rituximab is being tested for enhancement of selectivity [89].

CONCLUSION

Breast cancer is the malignancies with the highest prevalence and mortality rate in women, representing one of the key public health problems worldwide. Diagnostic and therapeutic progression in the last couple of decades improved prognosis for patients. However, further advances and novel strategies are needed for providing greater success of the therapeutic outcomes along with reduction of systemic toxicity; which besides direct effects influences patient's compliance. With a better understanding of breast cancer molecular basis and development of nanotechnology, novel innovative approaches started being extensively explored. Nanomedicine application could overcome various restrains that characterize conventional chemotherapeutic agents. Possibility for the administration of unstable agents opened a new field for pharmacotherapeutic consideration of siRNA, miRNA, genes, and peptides. Conventional therapies are being improved with encapsulation, as their pharmacokinetic properties are adjusted to better fulfill the safety and efficacy criteria. New targets are investigated for designing selective agents to treat aggressive types, metastases and multi-drug resistance, which could hardly be overwhelmed with conventional approaches. Additionally, considering their multi-functionality and almost infinite possibilities for modification, they are intensively tested for utilization in imaging and diagnostics, theranostics, tissue regeneration, as sensitizing and contrast agents. Therefore, nanomedicine-based research is widely distributed in the both pre-clinical and clinical setting and has promising chances of representing the future of breast cancer and other oncological treat-ments.

AUTHORS' CONTRIBUTIONS

Substantial contributions to the conception of the work were given by IT, MM and KS. IT has done the literature review and wrote the manuscript, which was critically reviewed by KS and MM for important intellectual content.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Primena nanomedicinskih tehnologija u terapiji karcinoma dojke

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KRATAK SADRŽAJ

Uvod: Uprkos napretku u terapiji maligniteta dojke, trenutno korišćene metode imaju brojne neželjene efekte, uzak terapijski indeks i nisku selektivnost, te dovode do sistemske toksičnosti uz istovremeno ograničenu efikasnost. Jedna od novih tehnologija koja bi mogla prevazići navedena ograničenja je primena nanotehnologije.

Tema: Inkorporacijom leka u nanonosač je omogućena administracija molekula koji imaju suboptimalni farmakokinetski profil kada se primenjuju kao slobodni agensi. Modifikacijom farmakokinetskih osobina i produžavanjem polu-života leka, nanomedicina može poboljšati bezbednosni profil trenutno korišćenih hemioterapeutika. Značajna karakteristika nanoterapije je mogućnost dizajniranja nosača leka sa selektivnom isporukom malignim ćelijama na osnovu njihovih diferencijalnih karakteristika.

Zaključak: Navedena prednost je inicirala potpuno novi segment razvoja ciljane terapije karcinoma dojke i dala obećavajuće rezultate čak i u tretmanu agresivnih tipova malignih tumora, metastaza i multiple rezistencije na lekove.

Ključne reči: karcinom dojke, nanomedicina, molekularna ciljana terapija, nanočestice, nosači lekova,