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Review

Emerging nanotherapeutic strategies in breast cancer

Elvin Blanco [a], Mauro Ferrari [a,b,*]

[a] Department of Nanomedicine, The Houston Methodist Hospital Research Institute, Houston, TX 77030, USA
[b] Department of Biomedical Engineering in Medicine, Weill Cornell Medical College of Cornell University, New York, NY 10021, USA

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ABSTRACT

Nanoparticle-based drug delivery platforms are emerging as powerful chemotherapeutic modalities in breast cancer. Doxorubicin and paclitaxel nanoparticle formulations are currently used clinically, yielding distinct pharmacokinetic parameters that prolong blood circulation times, enhance drug accumulation in tumors, and limit adverse side effects to patients. And while these nanoconstructs have shown substantial improvements in patient tolerability and survival, several emerging trends stand to make a significant impact on future generations of nanoparticle platforms for breast cancer therapy. Firstly, there is a heightened understanding of several processes involved in tumor growth, potentiation, and invasion, resulting in the identification of several attractive molecular targets. This in turn has given rise to antibody-based therapeutics, drug repositioning, and the burgeoning field of RNA interference (RNAi). Secondly, an enhanced understanding of transport phenomena involved in delivery of chemotherapeutics has led to a rethinking and retooling of nanoscale drug carrier designs. Nanoparticle platforms are now incorporating features meant to overcome biological barriers and enhance drug accumulation within tumors, all the while incorporating unique chemistries that enable for controlled release of therapeutic payloads. This review aims to detail the current clinical state of nanoparticle-based therapeutics in breast cancer, as well as highlight several platforms that exemplify the future generation of innovative approaches to chemotherapy in breast cancer.

Introduction

Despite considerable advances in breast cancer chemotherapy, mortality rates have remained relatively unaffected over the span of three decades [1]. Throughout this period, anthracyclines and taxanes have dominated the chemotherapeutic landscape, proving indispensable in several combination regimens [2]. Unfortunately, favorable patient outcomes have been largely overshadowed by severe morbidity. Cardiotoxicity following doxorubicin (DOX) administration has now been well documented [3], while paclitaxel (PTX) has been shown to result in hypersensitivity reactions and neuropathic pain [4]. The significant shortcomings associated with traditional formulations of chemotherapeutics arise predominantly from a lack of specificity. Firstly, drugs such as doxorubicin and paclitaxel possess mechanisms of action that fail to discriminate between malignant and noncancerous cells. Secondly, traditional chemotherapeutic formulations rely on excipient materials simply meant to increase drug solubilization. These vehicles fail to take into account critical pharmacokinetic parameters essential for enhanced drug accumulation and bioavailability within tumors. Regrettably, the adverse side effects resulting from this lack of specificity proves dose limiting, oftentimes precluding propitious response rates in patients and improvements in disease-free progression.

In the 1990's, two key events represented significant milestones towards more specific approaches to chemotherapy with regards to both drug transport and mechanism. The first was the FDA approval of liposomal doxorubicin (trade name: Doxil®) in 1995 for the treatment of Kaposi's sarcoma [5]. The second was the FDA approval in 1998 of trastuzumab (trade name: Herceptin®) for patients with human epidermal growth factor receptor 2 (HER2)-positive breast tumors [6]. These events represented highly reactionary departures from traditional chemotherapeutic practices of administering non-specific drugs, non-specifically. It then became clear that improvements in patient response could be achieved through the use of novel agents meant to target specific molecules or pathways either overexpressed or dysregulated in breast cancer, and through the use of improved delivery methods that guarantee

* Corresponding author. Department of Nanomedicine, The Houston Methodist Hospital Research Institute, 6670 Bertner St., M.S. R2-216, Houston, TX 77030, USA. Tel.: +1 713 441 8439; fax: +1 713 441 8235.
E-mail address: mferrari@tmhs.org (M. Ferrari).

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adequate accumulation of drugs in tumor tissue. Thus, these two events signaled a paradigmatic shift in breast cancer chemotherapy towards a more rational approach to tumor targeting with respect to cell killing and transport.

More than two decades after the discovery that HER2 was overexpressed in approximately one-fourth of breast cancer patients, chemotherapeutic regimens incorporating trastuzumab represent a standard of care for HER2-positive breast cancer patients [7]. Indeed there has been a recent surge in the understanding of several pathways and effectors of tumorigenesis, progression, and spread [8]. Consequently, this enhanced insight into molecular processes governing tumor growth has resulted in an abundance of potential targets for chemotherapy. As an example, the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (PI3K/Akt/mTOR) pathway plays a major role in cellular functions ranging from cell growth to proliferation to metabolism [9], with its activation also linked to HER2 and its family of receptors [10]. The PI3K/Akt/mTOR pathway has been found to be aberrantly activated in breast cancer, making agents that inhibit either PI3K, Akt, or mTOR attractive candidates for chemotherapy [11]. Therefore, several agents previously approved for other diseases are finding their way into chemotherapy regimens, undergoing what is known as repositioning. Moreover, the discovery of novel targets has led to the emergence of RNA interference (RNAi) via small interfering RNAs (siRNAs) for specific and efficient silencing of gene expression [12]. As the molecular portrait of breast cancer becomes clearer and more potential targets are identified, traditional chemotherapeutic strategies may give way to more personalized approaches to therapy.

Unfortunately, without special regard to precise delivery to tumors, novel agents in breast cancer will undoubtedly suffer the same fate as traditional chemotherapeutics. Limitations will continue to appear in the form of nonspecific distribution in healthy organs and tissues resulting in toxic side effects, and inadequate accumulation in tumors resulting in reduced efficacy. The FDA approval of liposomal doxorubicin demonstrated the distinct advantages afforded by nanoparticle constructs for chemotherapeutic drug delivery [13]. Nanoparticles such as liposomes and polymer micelles encapsulate drugs within a core, essentially increasing its solubility, protecting it from degradation, and preventing its premature release into the bloodstream [14]. The small size of nanoparticles, typically on the order of 10–100 nm assists in their evasion of the reticuloendothelial system (RES), resulting in longer circulation half-lives. The presence of poly(ethylene glycol) (PEG) on the surface of liposomes and other nanoparticles enables long-term circulation times in blood vessels [15]. Long circulation times and small size in turn aid in accumulation of nanoparticles in tumor tissues by extravasation through fenestrations present in tumor vasculature, a phenomenon known as the enhanced permeability and retention (EPR) effect [16]. The small size of nanoparticles also assists in their deep penetration within tumors [17], with impaired lymphatics resulting in prolonged retention.

In light of their numerous advantages, several nanoparticle platforms are currently being explored clinically in breast cancer. This review summarizes the present state of nanoparticle drug delivery in breast cancer, all the while intending to shed light on future strategies. This includes delivery of repositioned agents and genetic material, as well as novel strategies for controlled release of therapeutics and enhanced uptake in tumors. It is our belief that advances in molecular targeting of tumors cannot be realized without the enabling technology of nanoparticle delivery, and vice versa. Therefore, this review will highlight platforms that touch upon both of these trends, approaches that will usher in the realization of personalized treatments in breast cancer.

Nanoparticle platforms currently employed or explored clinically in breast cancer

Liposomes

Liposomes were initially described by Bangham and coworkers in 1964, and their potential for drug delivery reported a decade later [18]. Their spherical small size, typically on the order of 100 nm, proves ideal for long systemic circulation and enhanced accumulation in tumors through the EPR effect (Fig. 1A) [19]. The chemical composition of liposomes, an aqueous core surrounded by a phospholipid bilayer membrane, make them ideal carriers for different drugs of varying solubility, as water soluble drugs and genetic material such as genes and siRNA can be incorporated within the core while hydrophobic drugs can be housed within the membrane [20]. Incorporation of cholesterol within the bilayer not only aids in hydrophobic drug incorporation, but also maintains membrane bilayer stability [21]. Longer circulation lifetimes of liposomes can be obtained by incorporating PEG-lipid conjugates within the bilayer membrane [22].

As mentioned previously, liposomes became the first nanoparticle platform approved for systemic delivery of chemotherapeutics, proving pharmacokinetically superior than the conventional formulation in early clinical trials [5]. Encapsulating doxorubicin within PEGylated liposomes significantly increased the blood circulation time of the drug from a scale of minutes to days [23]. Importantly, liposomal doxorubicin substantially reduced cardiotoxicity associated with the drug [24]. In a Phase III trial comparing a 50 mg/m [2] dose of liposomal doxorubicin given every 4 weeks to a 60 mg/m [2] dose of conventional doxorubicin administered every 3 weeks, the risk of cardiotoxicity in metastatic breast cancer patients was significantly less in the liposomal group (4.7%) than in the group receiving the conventional formulation (19.6%) [25]. Moreover, no patients receiving liposomal doxorubicin presented clinical heart failure, in contrast to 4% of the patients in the conventional doxorubicin arm. These findings are similar to a Phase III trial reported by Harris et al., where cardiotoxicity events in metastatic breast cancer patients receiving liposomal doxorubicin were nearly half compared to those receiving the conventional drug formulation [26]. Reduced cardiotoxicity and clinical heart failure resulting from liposomal doxorubicin allowed for increases in mean cumulative doses of doxorubicin in patients before the appearance of adverse effects, allowing for improvements in antitumor responses, especially in combination with other chemotherapeutics. To highlight this, in a Phase III study that combined liposomal doxorubicin with docetaxel (DTX) in patients with advanced breast cancer, the combination resulted in improved progression free survival from 7 to 9.8 months [27]. Liposomal doxorubicin was also examined in a multicentre phase II study in combination with docetaxel and trastuzumab, with the treatment showing minimal cardiotoxicity, and demonstrated promising overall response rates in patients with metastatic breast cancer [28]. In a Phase I/II trial involving patients with locally advanced or metastatic breast cancer, liposomal doxorubicin was administered with trastuzumab and paclitaxel, after which the response rate was found to be 98.1% with a median time to progression of 22.1 months in metastatic patients [29].

Nanoparticle albumin-bound paclitaxel

Taxanes such as paclitaxel and docetaxel have recently become mainstay drugs in several adjuvant combination chemotherapy regimens, oftentimes supplanting anthracyclines and platinum-based agents [30]. Despite improvements in both disease free and overall survival of breast cancer patients following paclitaxel