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Review

A review on the efficacy and toxicity of different doxorubicin nanoparticles for targeted therapy in metastatic breast cancer

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ABSTRACT

In metastatic breast cancer (MBC), the conventional doxorubicin (DOX) has various problems due to lack of selectivity with subsequent therapeutic failure and adverse effects. DOX- induced cardiotoxicity is a major problem that necessitates the presence of new forms to decrease the risk of associated morbidity.

Nanoparticles (NPs) are considered an important approach to selectively increase drug accumulation inside tumor cells and thus decreasing the associated side effects. Tumor cells develop resistance to chemotherapeutic agents through multiple mechanisms, one of which is over expression of efflux transporters. Various NPs have been investigated to overcome efflux mediated resistance.

To date, only liposomal doxorubicin (LD) and pegylated liposomal doxorubicin (PLD) have entered phase II and III clinical trials and FDA- approved for clinical use in MBC. This review addresses the effects of LD and PLD on the hematological and palmar-plantar erythrodysesthesia (PPE) in anthracycline naïve and pretreated MBC patients. For evidence, studies to be included in this review were identified through PubMed, Cochrane and Google scholar databases. The results derived from: four phase III clinical trials that compared LD with the conventional DOX in naïve MBC patients, and ten non-comparative clinical trials investigated LD and PLD as monotherapy or combination in pretreated MBC. This work confirmed the cardiac tolerability profile of LD and PLD versus DOX, while hematological and skin toxicities were more common.

Other DOX-NPs in preclinical trials were discussed in a chronological order. Finally, the modern preclinical development framework for DOX includes exosomal DOX (exo-DOX). Exosomal NPs are non-toxic, non-immunogenic, and can be engineered to have high cargo loading capacity and targeting specificity. These NPs have not been investigated clinically. Our study shows that the full clinical potentiality of DOX-NPs remains to be addressed to move the field forward.

1. Introduction

The progressively increasing incidence of breast cancer is a major public health problem. It is the most common malignant disease affecting females by approximately 26% compared with other cancer types [1]. In Egypt, incidence rates in females reached 38.8% [2]. Doxorubicin (DOX) is one of the main treatments for early and advanced breast cancer. The induced cardiotoxicity necessitates the presence of new forms to decrease the risk of drug associated morbidity [3].

In early-stage breast cancer, surgery alone can cure the patient, later adjuvant chemotherapeutic agents are planned to treat micro-metastatic stages [4]. Metastatic breast cancer (MBC) and recurrent cases were approached systemically to target the areas affected by the disease. Hormonal therapy and chemotherapy are the main systemic interventions [5]. Hormonal therapy is for estrogen and/or progesterone–positive diseased patients without a life-threatening metastasis. Patients who develop resistance to hormonal treatment become candidates for cytotoxic chemotherapy [5].

The therapeutic goal in treating MBC is to prolong the survival while maintaining a good quality of life. Chemotherapy is usually initiated as a monotherapy, but combination therapy is preferred as it has

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higher response rates (RR) and early onset of clinical benefits [6].

The aim of the present review is to take a journey through the history of different doxorubicin nanoparticles (DOX-NPs) passing through the conventional DOX and exploring the potential new DOX-NPs based therapy for treating MBC. Nanotechnology is a promising alternative that has been developed to overcome limitations in cancer therapy.

This review includes an updated summary of the clinical and preclinical studies with various DOX-NPs based therapy in metastatic breast cancer, presented in a chronological order. Previous systematic reviews have demonstrated the efficacy and cardiac safety of LD (liposomal doxorubicin) and PLD (pegylated liposomal doxorubicin) [8]. To our knowledge, there are currently no available reviews to address the effects of LD and PLD on the hematological and palmar plantar erythrodysesthesia (PPE) in anthracycline naïve and pretreated MBC. For evidence, the current review involved studies that were identified through PubMed, Cochrane and Google scholar database.

2. Conventional doxorubicin and its limitation

Doxorubicin (DOX) is one of anthracycline family of antibiotics [9]. Two proposed mechanisms for DOX anticancer effect are confirmed. First mechanism is by intercalation into DNA and the subsequent disruption of topoisomerase-II-mediated DNA repair for which candidate pharmacogenes are TOP2A, MLH1, MSH2, TP53, and ERCC2 genes [10] (Fig. 1). Second mechanism involves oxidative stress to cellular membranes, DNA and proteins [11] for which candidate genes involve NADH dehydrogenases, nitric oxide synthases, xanthine oxidase, glutathione peroxidase, catalase and superoxide dismutase [12].

DOX clinical uses have been restricted due to dose-dependent cardiotoxicity. Initial subclinical myocardial cell injury is followed by asymptomatic decline in left ventricular ejection fraction (LVEF) then finally progresses to symptomatic heart failure, if left untreated. The prevalence of heart failure was estimated to be 5%, 26% and 48% in patient at doses of 400, 550 and 700 mg/m^2 respectively [13]. This heart failure could present as either early-onset occurring within 2–3 days after administration or late-onset cardiotoxicity [14].

Risk factors for DOX cardiotoxicity include a prior history of congestive heart failure, left ventricular ejection fraction (LVEF) less than 50%, previous cardiac disease, hypertension [15], a cumulative dose > 550 mg/m^2, age greater than 70, female sex [16] and combination therapy with other cardiotoxic chemotherapy as trastuzumab. Not all patients develop cardiac events as genetic factors interfere in the individual cardiac response to DOX. An association between genetic variants in mitochondrial NADPH oxidase complex genes and doxorubicin cardiotoxicity is an example for genetic variations-associated individual susceptibility to DOX-induced oxidative stress [17].

Other conventional DOX toxicities include myelosuppression, acute nausea and vomiting, alopecia, stomatitis and extravasation reactions [18]. The emergence of multidrug resistance and the low specificity against cancer cells are additional problems with DOX usage. To minimize the toxicity, anthracycline analogues such as epirubicin have received much attention. However, cardiac toxicity has remained the limiting factor for using these analogues in patients with MBC [19].

3. Nanoparticle doxorubicin-based therapy in metastatic cancer

Nanotechnology is a promising alternative to overcome different limitations in cancer therapy. Several nanoparticles (NPs; diameter 1–100 nm) carrying multiple drugs have been investigated regarding anticancer activities. NPs are characterized by the presence of high ligand density on the surface due to their high surface-area-to-volume ratio. They also increase local drug concentration by carrying the drug within and control its release upon reaching the targets [20,21].

As illustrated in Fig. 2, DOX- NPs typically fall into three categories: (a) inorganic NPs (e.g., gold, iron oxide, etc.), (b) organic NPs (e.g., polymeric, liposomes, micelles, etc.) and (c) integrated NPs. Inorganic DOX-NPs have been investigated for efficacy in preclinical studies, but are yet to be evaluated clinically. Conversely, organic DOX-NPs have exhibited success in the clinical studies where they are currently being developed for broad applications in MBC [7]. To date, only LD and PLD have entered Phase II and III clinical trials and were approved for

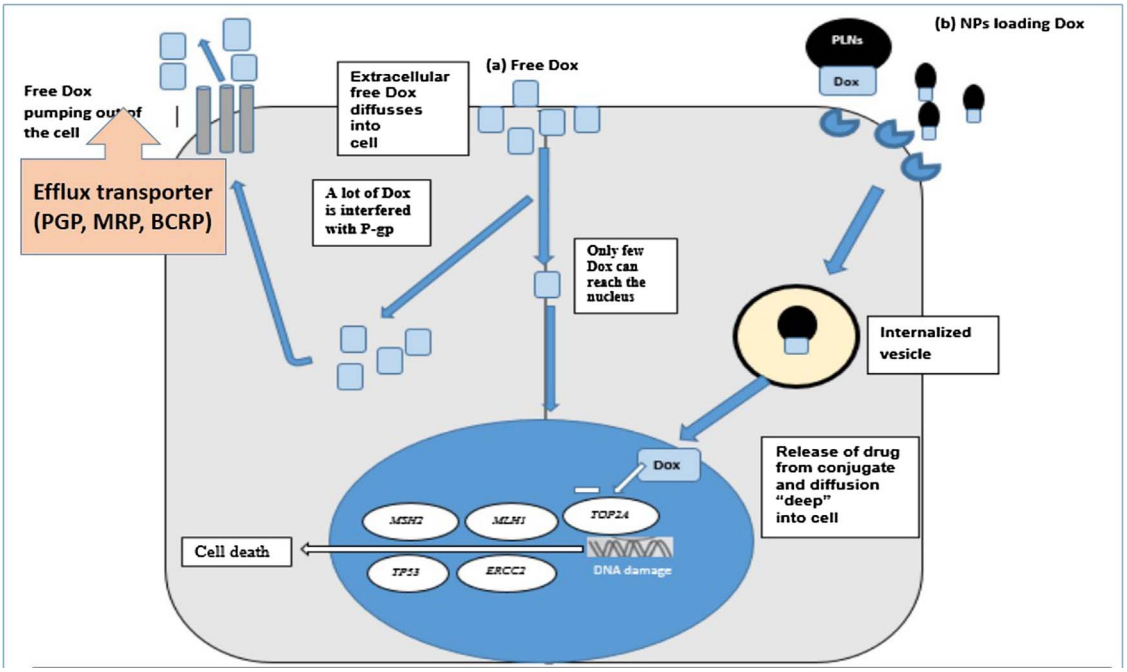

Fig. 1. The proposed mechanism of enhanced antitumour activity of PLD in breast cancer cells that overexpress efflux pumps. MDR genes produce three main types of efflux proteins: P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP) and BC resistance protein (BCRP). Such efflux proteins play a key role in protecting cells against doxorubicin.
A. Some of the drug molecule that diffuse into the cells are removed by the p-gp
B. Endocytosis of PLD, that re difficult to be cleared from breast cancer cells by p-gp