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Invited review

New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy

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ABSTRACT

We herein review various pharmacological and clinical aspects of pegylated liposomal doxorubicin (PLD), the first nanomedicine to be approved for cancer therapy, and discuss the gap between its potent antitumor activity in preclinical studies and its comparatively modest achievements in clinical studies and limited use in clinical practice. PLD is a complex formulation of doxorubicin based on pharmaceutical nanotechnology with unique pharmacokinetic and pharmacodynamic properties. Its long circulation time with stable retention of the payload and its accumulation in tumors with high vascular permeability both result in important advantages over conventional chemotherapy. The ability of PLD to buffer a number of undesirable side effects of doxorubicin, including a major risk reduction in cardiac toxicity, is now well-established and confers a major added value in a number of disease conditions. PLD is approved for the treatment of ovarian cancer, breast cancer, multiple myeloma, and Kaposi sarcoma. In addition, clinically significant antitumor activity of PLD has been reported in a number of other cancer types, including lymphomas and soft tissue sarcomas. In spite of this, PLD has not replaced conventional doxorubicin in common applications such as the adjuvant and neoadjuvant treatment of breast cancer, and its use in the clinic has not become as widespread as one may have predicted. Exploiting the unique pharmacology of PLD, analyzing its selective biodistribution and homing to tumors in cancer patients with proper theranostic tools, and harnessing its complex interaction with the immune system, will lead to a more selective and rational use of PLD that may have great impact on future clinical results and may help realize its largely untapped potential.

Contents

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1. Introduction

Pegylated liposomal doxorubicin (PLD)[1] was approved for clinical use by the FDA in November 1994 and became *de facto* the first cancer nanomedicine. Despite these two decades of clinical experience, we are still discovering many unique properties and unexpected clinical responses of this peculiar reformulation of doxorubicin. As of today, the clinical achievements have been important but still modest and by far less than predicted by preclinical studies (Petersen et al., 2016). This gap between expectations based on laboratory models and clinical achievements is relevant to most nanomedicines (Lammers et al., 2012).

In this review, we focus on new insights on the mechanism of action of PLD and evaluate retrospectively whether the clinical development took the correct path or may have missed important signals. Our analysis reveals that there is a high likelihood that the clinical potential of PLD was significantly underestimated by various deficiencies or flaws in clinical design, and that immunological aspects and imaging-guided patient selection may play an important role in defining a more effective use of PLD. We do not attempt to review comprehensively the preclinical and clinical data with PLD, as the cumulative amount of information in the last 25 years in this field is staggering, and this exhaustive exercise will not add any specific value to the multiple reviews already published. Lastly, our underlying message is that PLD-based therapies have a significant wealth of untapped potential for improved clinical results.

1.1. Doxorubicin

Doxorubicin, also known as adriamycin, is the most widely used anthracycline, and has demonstrated significant therapeutic activity in many cancer types, being regarded as one of the most potent chemotherapeutic drug approved (Carvalho et al., 2009). Nevertheless, its use is limited by a problematic toxicity profile, particularly cumulative cardiotoxicity. Doxorubicin is composed of a fluorescent tetracyclic chromophore (doxorubicinone or adriamycinone), linked to a positively charged aminosugar (daunosamine). Doxorubicin enters the cell by a flip-flop based diffusion across the plasma membrane (Regev et al., 2005) followed by translocation through the nuclear pore complexes into the nucleus. Although doxorubicin interacts with and deranges many cellular processes, the most well accepted mechanism of antitumor effect is the inhibition of DNA topoisomerase II. Following intercalation of its planar rings in the minor groove of the DNA double helix, doxorubicin stabilizes the topoisomerase II-DNA complex, inhibiting the progression of the S-phase of the cell cycle. The topoisomerase II-doxorubicin-DNA complex can induce DNA double strand breaks. A recent study reported doxorubicin's ability to intercalate with not only nuclear DNA, but also mitochondrial DNA (Ashley and Poulton, 2009).

Additionally, doxorubicin interacts with mitochondria, through its affinity with the mitochondrial lipid cardiolipin, and with intracellular iron generating highly reactive oxygen species (ROS). Free radicals are responsible for the cardiotoxicity elicited by the drug, though these same mechanisms may contribute to the doxorubicin antitumor effect (Gewirtz, 1999; Minotti et al., 2004). Anthracycline-induced cardiomyocyte damage has been generally attributed to the production of toxic ROS and an increase in oxidative stress, which among various deleterious effects also cause lipid peroxidation of membranes (Singal et al., 1997). Cardiomyocytes are much more sensitive to the oxidative stress caused by doxorubicin because of their high reliance on oxidative substrate metabolism and the high fraction of cardiomyocyte volume made up by mitochondria compared to tumor cells. In fact, oxidative damage by doxorubicin in tumor cells is only seen at very high doxorubicin concentrations (Minotti et al., 2004). The generation of ROS by doxorubicin in cardiomyocytes is enhanced by the presence of intracellular non-chelated iron (Kotamraju et al., 2004). This is the basis for the use of an intracellular iron chelator, dexrazoxane, to prevent cardiotoxicity of doxorubicin (Seifert et al., 1994).

Unfortunately doxorubicin is not specifically targeted to any tumor molecular marker or driver, and it can affect the growth and function of many cell types in the body. The severity of side effects and their occurrence depends on the dosage and schedule of doxorubicin. Furthermore, its pharmacokinetics is characterized by a very short half-life in circulation with extensive, non-selective, tissue distribution. Tumor doxorubicin levels in mouse models hardly reach peak levels of 2% of the injected dose per gram (%ID/g) tumor (Gabizon et al., 1996). Therefore, as with many other anti-cancer agents, effective therapy with doxorubicin will often require high doses, which can further aggravate adverse toxic side effects due to the lack of selectivity of this drug.

1.2. Pegylated liposomal doxorubicin—the product

Pegylated (polyethylene glycol coated) liposomal doxorubicin (PLD), also known as Doxil, Caelyx or, in its FDA-approved generic version, Lipodox, was the first FDA-approved cancer nanomedicine, (Barenholz, 2012), and is indicated for HIV-related Kaposi's sarcoma, advanced ovarian cancer, metastatic breast cancer, and multiple myeloma (Duggan and Keating, 2011). PLD, together with nanoparticle albumin-bound paclitaxel (NAB-paclitaxel) are probably the cancer nanomedicines that have made the most important clinical impact, excluding antibody-drug conjugates which are generally considered as a separate group of complex drugs. In addition to PLD, other liposomal products with the anthracycline as an active component approved by the FDA or by EMA for cancer therapy include DaunoXome© (Gilead) and Myocet© (Teva).

[1] PLD is commercially known as Doxil®, Caelyx® or by its US generic name, Lipodox.