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COMMENTARY

Liposomal doxorubicin: the good, the bad and the not-so-ugly

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ABSTRACT

There are direct and indirect indications that PEGylated liposomal doxorubicin (Doxil), a widely used anticancer nanomedicine, has a subclinical immune suppressive effect. As an example of a seemingly bad pharmacological property turning out to be "not-so-ugly", but actually beneficial, the authors highlight the potential benefits of Doxil's immune suppressive effect. These include (1) the decreased uptake of the drug by the MPS which may entail enhanced tumor uptake, and, hence, improved therapeutic efficacy; (2) the use of slow infusion protocols in reducing the risk of hypersensitivity (infusion) reactions; and (3), possible protection against hypersensitivity reactions to co-administered reactogenic drugs. To consider immune suppression as useful represents a paradigm shifts in nanotoxicology and anticancer chemotherapy.

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Introduction

The authors know and highly appreciate Peter Cullis' life-long scientific and entrepreneurial contribution to the liposome field. That is why they felt that they should participate in this 'celebration' issue. We wish to do that with reference to the title of a 1966 epic motion picture (likely watched by Peter in his early career) seen as a highly influential example of the western film genre and one of the greatest films of all times. However, alluding to Peter's reputation in our field as an innovator who can turn ugly to 'not-so-ugly', we paraphrased the movie's title as it is now. Peter and his team in Vancouver, BC are well known for the essential roles they played in the clinical development of the approved liposomal drugs Abelcet, Myocet and Marqibo, and many more novel formulations that are now in clinical testing against cancer, cystic fibrosis, anthrax, amyloidosis atherosclerosis and other diseases. Nevertheless, perhaps less recognized is Peter's pivotal contribution to choosing or developing safe cationic (phospho)lipids from among many toxic – and thus 'ugly' – cationic lipids, which became essential components of lipid nanoparticles (LNPs) used today for nucleic acid (siRNA) delivery. By such turning 'ugly' into 'not-so-ugly' Peter helped initiate a paradigm shift in the liposome field in terms of lipid toxicity. This kind of paradigm shift reminds us of a recent story that tells the discovery of the benefits of a toxic property of liposomal doxorubicin (Doxil), a story to which the authors themselves had original contributions [1,2].

Doxil – the good and bad

The liposomal doxorubicin product Doxil (in Europe named Caelyx) is the first approved oncological nanodrug approved by the FDA (1995). There is huge literature dealing with its benefits, unique properties, mechanism of action, clinical efficacy and adverse effects [3,4]. In a nutshell, it is the most widely used anticancer liposome formulation which, besides its original approval against Kaposi's sarcoma and platinum-resistant ovarian cancer, has also been approved for multiple myeloma and is widely used against breast cancer either alone, or in combination with other cytostatic agents. This success is based on the prolonged circulation time of unilamellar PEGylated liposomes with a mean size around 100 nm, which enables increased uptake by tumors via the enhanced permeability and retention (EPR) effect. Its most conspicuous benefit over free drug, however, is the strong reduction of the cardiotoxicity of doxorubicin, likely a result of the inability of the liposomal encapsulated drug to enter the heart. Doxil is also credited with the reduction of other systemic side effects of the cytostatic agent, such as for example hair loss and nausea. Nevertheless, the encapsulation of doxorubicin in liposomes can also entail novel toxicities, namely the palmar–plantar erythrodysesthesia (hand–foot syndrome) [5] and the increased occurrence of acute hypersensitivity (infusion) reactions referred to as complement activation-related pseudoallergy (CARPA) [6–8].

CARPA is an immune side effect that can actually occur with the majority of nanoparticles when administered intravenously. Although the risk of CARPA can be minimized by applying immune suppressive drugs (e.g., steroids), antihistamines, non-reactogenic infusion protocols [8–10] and immune prophylaxis [11], full protection against the rare occurrence of severe, potentially lethal reactions has not yet been achieved either with Doxil [12] or other reactogenic drugs.

Doxil – the not-so-ugly

Immune suppression, in theory, can be very ugly for cancer patients who can become more prone to systemic infections. As discussed below, there is experimental and indirect clinical

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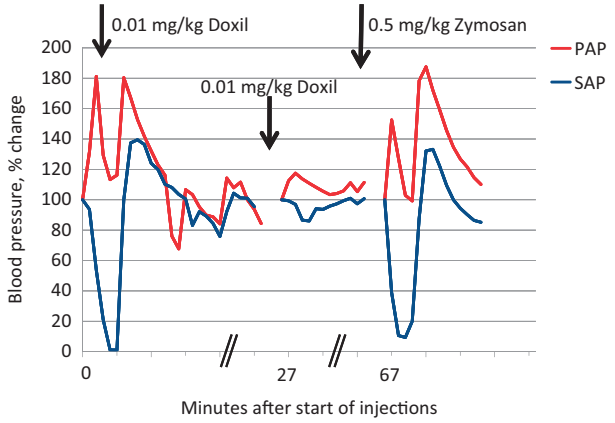

Figure 1. Doxil-induced tachyphylaxis in pigs, a model of liposome-induced hypersensitivity reactions [17]. Bolus injection of a tiny amount of Doxil (0.01 mg phospholipid/kg) caused dramatic blood pressure changes within 3 min, manifested in maximal rise and drop of pulmonary and systemic arterial pressures (PAP and SAP), respectively. The reaction to a repeated identical dose 27 min later was negligible. Nevertheless, the animal retained reactivity to the control zymosan indicated functional immune response. Figure reproduced from Ref. [6] with permission.

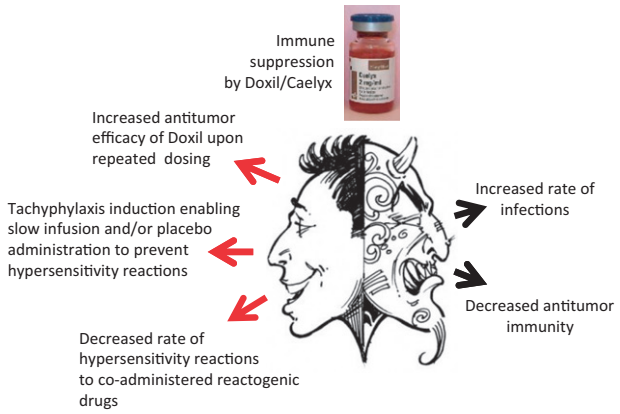

Figure 2. The Janus-face of immune suppression by Doxil/Caelyx.

evidence that Doxil can cause immune suppression, but fortunately this side effect does not seem to be a clinical problem as evidenced by the large number (>600,000) of patients treated with Doxil [10] without a reported increase in infection rate [12].

The experimental evidence for immune suppression was found in rats, wherein Doxil led to impairment of the function of the mononuclear phagocyte system (MPS) and substantial depletion of liver macrophage populations. Nevertheless, consistent with the apparent lack of a problem in Doxil-treated patients, the bacterial clearance capacity of the animals' MPS was not impaired when Doxil was administered in a regimen that resembled the clinical setting [1].

Indirect indications of Doxil-induced immune suppression include the dose-dependent pharmacokinetics of Doxil, resulting in slower clearance and a disproportional increase of tumor uptake at higher doses (in the 2.5–20 mg/kg range) [13]. Such a deceleration of clearance was not seen with free doxorubicin administration at a similar dose or when doxorubicin-free liposomes were co-administered with free doxorubicin [13]. Moreover, the $T_{1/2}$ of Doxil rises after repeated administrations in man [14], which can also be explained by MPS suppression.

Another indirect experimental *in vivo* observation pointing to the presence of a rapid immune suppressive effect of Doxil is the phenomenon called tachyphylaxis, whereupon the hypersensitivity reaction caused by the first bolus of Doxil is decreased or absent upon the second or repeated administration of the same, or even an increased dose [11] (Figure 1). The phenomenon has nothing to do with intraliposomal doxorubicin, as can be observed with many other liposomes in pigs and rats [15–17]. Its equivalent in man is the slow initial infusion of Doxil at a speed that prevents the hypersensitivity reaction to the drug administered in the rest of the infusion [6,12].

Another clear indication for immune suppression by Doxil comes from a clinical study wherein 'Doxil plus carboplatin' therapy was compared with 'carboplatin only' therapy in patients with ovarian and peritoneal carcinoma. The authors unexpectedly observed a significant suppression of the allergic reactions to carboplatin by Doxil [18]. Based on these data, the potentially 'ugly' immune suppression by Doxil, likely occurring at the level of MPS macrophages, turns out to be 'not-so-ugly' as it leads to clinical benefits. One such benefit is that tumor uptake and therapeutic efficacy of Doxil might increase upon repeated dosing as a result of less efficient uptake by MPS macrophages, leading to a longer circulation time (as seen with dose escalation in mice [14]. Another benefit is that Doxil may provide therapeutic advantage over paclitaxel or gemcitabine in combination chemotherapies with carboplatin, as hypersensitivity reactions to carboplatin have become dose-limiting to its clinical use. The short-term, non-active immune suppression that underlies Doxil's self-restricting reactogenicity is also beneficial as it enables the prevention of hypersensitivity reactions by way of slow infusion and/or Doxebo prophylaxis [10,11].

Thus, immune toxicity by liposomes is a Janus-faced phenomenon; it can be harmful, but at the same time beneficial (Figure 2); example of a *para*digm shifting *para*Dox in nanopharmacology and toxicology.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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