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Review Article

Extracorporeal apheresis system – A nanoparticle drugs' elimination method to enhance the benefit of cytostatic therapy in cancer patients

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ARTICLE INFO

Article history:
Received 30 October 2015
Accepted 9 November 2015
Available online 22 November 2015

Keywords:
Liposomal doxorubicin
Plasma filtration
Toxicity
Drug delivery system

ABSTRACT

Cytostatic treatment is often negatively affected by dose-limited toxicities. Novel agents, including nanoparticle-based drug delivery systems (DDS), are becoming available to overcome this problem. Despite achieving a lesser toxicity in exchange for more favorable pharmacokinetic profiles, the use of DDS is often associated with a particular toxicity profile. The accumulation of DDS in tumor tissue is much faster than in normal tissues where toxic events occur. While only a small amount of DDS is delivered to the target tissue, and accumulated there, most of the administered dose remains in circulation. The removal of this fraction, which is no longer effective, is thought to reduce toxicity. Pegylated liposomal doxorubicin (PLD) has been proven to be effective in platinum-resistant ovarian carcinoma with the reduced risk for cardiotoxicity. Once saturation in tumor tissue is achieved, prolonged circulation seems ineffective, whereas other toxicity risks (palmar-plantar erythrody sesthesia and mucositis) have been reported. Therefore, extracorporeal elimination of circulating nanoparticles using plasma filtration would probably reduce this risk of toxicity. The elimination rate could be kinetically regulated, i.e. based on individual doxorubicin pharmacokinetic variables. Plasma filtration can significantly influence the exposure to PLD (plasma concentration-time profile-AUC of PLD) and would be a suitable, well tolerated method enabling individualized, more effective and safer chemotherapy.

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1214-021X/$ – see front matter
http://dx.doi.org/10.1016/j.jab.2015.11.002

Introduction

Cytostatic treatment is often negatively affected by dose-limited toxicity. Novel agents, including nanoparticle-based drug delivery systems (DDS), are now available to overcome this problem. Encapsulated cytostatic drugs, such as doxorubicin, cisplatin, taxol or ellipticine, are an effective tool in cancer treatment (Sempkowski et al., 2014; Li et al., 2015; Andey et al., 2015). Their effect involves the growth arrest of cancer cells, but their effect is often non-specific and operates also on healthy cells. The toxicity of cytostatic drugs causes severe side effects and is therefore a key problem restraining the full use of their therapeutic potential. For this reason, the current trend aims to encapsulate drugs inside complex delivery structures such as proteins, micelles or liposomes. An example of this could be pegylated liposmal doxorubicin (PLD), which has been in use for a long time in our therapeutic protocols in the treatment of platinum-resistant ovarian cancer (Kubeček et al., 2015).

Pegylated liposomal doxorubicin (PLD)

Pegylated liposomal doxorubicin (PLD) is a formulation based on the anthracycline antibiotic doxorubicin, encapsulated in polyethylene-glycol (PEG) coated liposomes. Liposomes are small vesicles composed of a lipid bilayer membrane with an aqueous core with an average size of 90–100 nm. The surface of the liposomes is covered with a dense layer of PEG covalently attached to the lipid membrane in a process called pegylation (Papahadjopoulos et al., 1991; Gabizon et al., 2003; Wagner and Vorauer-Uhl, 2011). This formulation leads to a significant change in the toxicity profile and pharmacokinetic properties of the parent drug. PLD is currently approved for the treatment of AIDS-related Kaposi's sarcoma, metastatic breast cancer, multiple myeloma, and metastatic ovarian cancer (Marchal et al., 2015).

The pharmacokinetics of conventional and liposomal doxorubicin is quite different. Pegylated doxorubicin pharmacokinetics results in extremely prolonged residence time in circulation as compared against non-pegylated doxorubicin (Gabizon et al., 2008). The half-life of PLD is calculated around 55 h.

PLD has a very low absorption in the mononuclear phagocyte system (Skeleton et al., 2002). Mainly because of the polyethylene glycol layer surrounding the doxorubicin containing liposomes. Doxorubicin is eliminated mostly by the liver. Approximately 90% of doxorubicin remains in circulation in encapsulated form since it is only released when retained in the tumor (Gabizon et al., 2012). Although the exact mechanism of antineoplastic agents release from liposomes is not well understood, they are likely to proceed in the same manner as endocytosis, degraded within lysosomes thus releasing their content, or by lipid exchange between liposomes and cell membrane leading to the transfer of their content into the cells, or by the fusion of liposomes with the cell membrane. Liposomes also can connect to the cell surface, allowing their content to penetrate through the cell membrane into the cytoplasm; for example – concentration of PLD in Kaposi's sarcoma lesions can be up to 22 times higher than in normal tissue (Amantea et al., 1997; D'Amico et al., 2010).

Adverse effects and toxicity

Liposomes tend to accumulate at sites of inflammation and in vascularized tumor tissue with a fenestrated endothelium, whereas in normal parenchymal organs with intact and tight endothelial barrier their concentration is lower. This explains the reduced cardiotoxicity of this PLD formulation (Xing et al., 2015). Myelotoxicity presents a similar behavior because the liposomes are taken up by the reticuloendothelial system (O'Brien, 2008; Staropoli et al., 2014).

The toxicological profile of PLD is quite different from that of free doxorubicin regarding palmar-plantar erythrodysesthesia (PPE, also called hand-foot syndrome) and mucositis, which are the most common adverse effects (Uziely et al., 1995). Despite not being life-threatening, these side effects might, in severe cases, lead to dose reduction or chemotherapy cycle postponement, thus influencing therapy outcome in a negative manner (Lotem et al., 2000).

Mechanism of action: Liposome released doxorubicin is also responsible for the formation of reactive oxygen species (ROS) that induce the production of chemokines and pro-inflammatory cytokines (IL-1β, IL-6 a IL-1α) in keratinocytes (Sinha et al., 1987). These mediators are responsible for leucocyte chemotaxis and inflammatory reaction enhancement. Moreover, ROS can cause direct damage to collagen fibers. In affected areas, the combination of an inflammatory reaction, keratinocytes' apoptosis and collagen degradation lead to complete skin destruction in the affected areas (Yokomichi et al., 2013).

Mucositis: Mucositis usually occurs as stomatitis, but rare cases of pharyngo-esophagitis and vulvo-vaginitis were also described (Soloman and Gabizon, 2008). The incidence of mucositis is mainly affected by the amount of PLD administered as a single dose, unlike PPE which is rather associated with dose intensity – dose/time interval between drug administrations (Lyass et al., 2000).

PPE: The syndrome culminates as painful erythema and swelling, predominantly in areas exposed to pressure such as hand palms and feet soles, followed by skin desquamation and re-epithelization (Fig. 1). The severity may vary from the development of mild erythema to severe skin damage causing contemporary invalidity of the patient. However, skin affection is temporary with a complete restitution after 2–3 weeks (Gabizon, 2001). Therefore, dose reduction seems to be a reasonable approach to reduce the incidence of stomatitis, but has a little impact in on PPE prevention. On the other hand, PPE

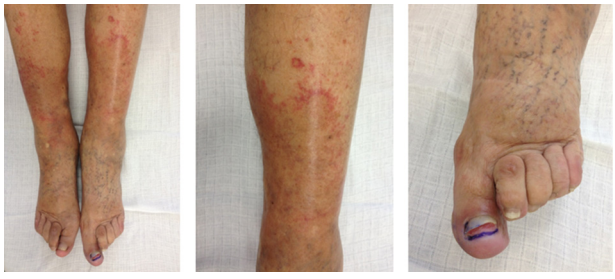

Fig. 1 – Patient – female, 46-year old (at the time of study), with palmar-plantar erythrodysesthesia (PPE, also called hand-foot syndrome). PPE is the most common sign of cutaneous toxicity of PLD (adverse effects).