Journal of Controlled Release 163 (2012) 322–334

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Liposomal paclitaxel formulations

Štěpán Koudelka [a], Jaroslav Turánek [a,b,*]

[a] Department of Toxicology, Pharmacology and Immunotherapy, Veterinary Research Institute, Brno, Czech Republic
[b] Department of Pharmacology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

ARTICLE INFO

Article history:
Received 14 May 2012
Accepted 7 September 2012
Available online 15 September 2012

Keywords:
Paclitaxel
Liposome
Drug targeting
Drug delivery systems
Anti-cancer drugs

ABSTRACT

Over the past three decades, taxanes represent one of the most important new classes of drugs approved in oncology. Paclitaxel (PTX), the prototype of this class, is an anti-cancer drug approved for the treatment of breast and ovarian cancer. However, notwithstanding a suitable premedication, present-day chemotherapy employing a commercial preparation of PTX (Taxol®) is associated with serious side effects and hypersensitivity reactions. Liposomes represent advanced and versatile delivery systems for drugs. Generally, both in vivo mice tumor models and human clinical trials demonstrated that liposomal PTX formulations significantly increase a maximum tolerated dose (MTD) of PTX which outperform that for Taxol®. Liposomal PTX formulations are in various stages of clinical trials. LEP-ETU (NeoPharm) and EndoTAG®-1 (Medigene) have reached the phase II of the clinical trials; Lipusu® (Luye Pharma Group) has already been commercialized.
Present achievements in the preparation of various liposomal formulations of PTX, the development of targeted liposomal PTX systems and the progress in clinical testing of liposomal PTX are discussed in this review summarizing about 30 years of liposomal PTX development.

Contents

Abbreviations: Cr-P, paclitaxel solubilized in Cremophor EL®; DCP, dicetylphosphate; DEPC, dielaidoyl phosphatidyl choline; DLPC, dilauroyl phosphatidyl choline; DLPE, dilauroyl phosphatidyl ethanolamine; DLPG, dilauroyl phosphatidyl glycerol; DLTs, dose-limiting toxicities; DMPC, dimyristoyl phosphatidyl choline; DMPG, dimyristoyl phosphatidyl glycerol; DOTAP, dioleoyl trimethylammonium propane; DOPC, dioleolyl phosphatidyl choline; DPPC, dipalmitoyl phosphatidyl choline; DSPE-PEG, distearoyl phosphatidyl ethanolamine-polyethylene glycol; DSPE-mPEG, distearoyl phosphatidyl ethanolamine-methoxy polyethylene glycol; EPC, egg phosphatidyl choline; EPR, enhanced permeability and retention; FA, folic acid; FDA, Food and Drug Administration; FGF(s), fibroblast growth factor(s); FR, folate receptor; HA, hyaluronic acid; HEPC, hydrogenated egg phosphatidyl choline; HER-2, human epidermal growth factor receptor-2; HCC, hepatocellular carcinoma; HSPC, hydrogenated soybean phosphatidyl choline; HUVEC, human umbilical vein endothelial cells; *i.v.*, intravenous; *i.p.*, intraperitoneal; IRRs, infusion-related reactions; LEP, liposome-encapsulated paclitaxel; LEP-ETU, liposome-encapsulated paclitaxel formulation developed and marked by NeoPharm; MOPC, oleoyl-hydroxy phosphatidyl choline; MLV(s), multilamellar vesicle(s); MRI, magnetic resonance imaging; MTD(s), maximum tolerated dose(s); NRP-1, neurolipin-1; NSCLC, non-small cell lung cancer; OQLCS, octadecyl-quaternized lysine-modified chitosan; PC, phosphatidyl choline; PEG, polyethylene glycol; PG, phosphatidyl glycerol; PL(s), phospholipid(s); POPG, palmitoyl-oleoyl phosphatidyl choline; PRC, People's Republic of China; PTX, paclitaxel; RD, recommended dose; RES, reticuloendothelial system; RHAMM, receptor for hyaluronan-mediated mobility; SCID, severe combined immunodeficiency; SCPC, stearoyl-capryoyl phosphatidyl choline; SOPC, stearoyl-oleoyl phosphatidyl choline; α-TAS, α-tocopheryl acid succinate; TATp, transactivating transcriptional activator peptide.

* Corresponding author at: Department of Toxicology, Pharmacology and Immunotherapy, Veterinary Research Institute, Hudcova 70, 621 00 Brno, Czech Republic. Tel.: +420 533 331 311.
E-mail address: turanek@vri.cz (J. Turánek).

0168-3659/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jconrel.2012.09.006

1. Introduction

Taxanes are complexes of diterpenoid natural products and semi-synthetic analogs. Presently, these drugs belong to prominent anti-cancer agents used for combined chemotherapy [1]. Paclitaxel (Fig. 1) (PTX, the chemical name is 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine), the prototype of this class, emerges from a natural source [2]. This drug is approved for the treatment of breast and ovarian cancer. PTX was found to be effective in treating a broad spectrum of advanced human cancer including breast and ovarian cancer as well as non-small cell lung carcinoma (NSCLC), melanoma and head and neck cancer (see for review) [3].

The commercial PTX preparation (Taxol®) is formulated in the vehicle composed of Cremophor EL® (polyethoxylated castor oil used as a solubilizing surfactant) and dehydrated ethanol, which provides a homogeneous preparation. In the clinical application, PTX is usually administered as a 3-hour and 24-hour infusion representing a total dose of 135–175 mg/m^2 of the body every 3 weeks [4]. However, the present-day chemotherapy employing Taxol® is accompanied by serious problems. One of the major problems associated with this formulation is the fact, that the diluted Cremophor EL®/ethanol vehicle is toxic [5]. The negative side effects include serious hypersensitivity reactions, nephrotoxicity and neurotoxicity [6]. PTX solubilized in Cremophor EL® (Cr-P) shows also an incompatibility with the plastic components of the administration sets [7,8]. Furthermore, the short-term stability of PTX upon dilution with aqueous media can result in possible drug precipitation [9].

It follows that the clinical application of Taxol® is connected with problems of incompatibility and instability. Special requirements regarding a proper filter device as well as appropriate containers and infusion bags for the storage and administration of the drug have to be fulfilled.

2. Solubilization and delivery systems for paclitaxel

Present-day cancer chemotherapy with PTX is associated with hypersensitivity reactions in spite of a suitable premedication with corticosteroids and anti-histamines [3]. Hence, the development of an improved delivery system for PTX is of high importance. Current approaches to the improvement are focused mainly on the development of formulations that are devoid of Cremophor EL®, investigation of the possibility of a large-scale preparation and a request for a longer-term stability. These different approaches have shown some promising possibilities to replace Taxol® by a less irritable preparation such as: (a) micelle formulations [10], (b) water-soluble prodrug preparations [11], (c) enzyme-activatable prodrug preparations conjugated with antibodies or albumin [12,13], (d) parenteral emulsions [14], (e) microspheres [14,15], (f) cyclodextrins [16], and (g) nanocrystals [17]. Only Abraxane® (albumin nanoparticle-based PTX preparation) and Lipusu® (liposomal PTX approved by State FDA of China) have entered the field of clinical applications. Generally, liposomes and protein nanoparticles represent a promising

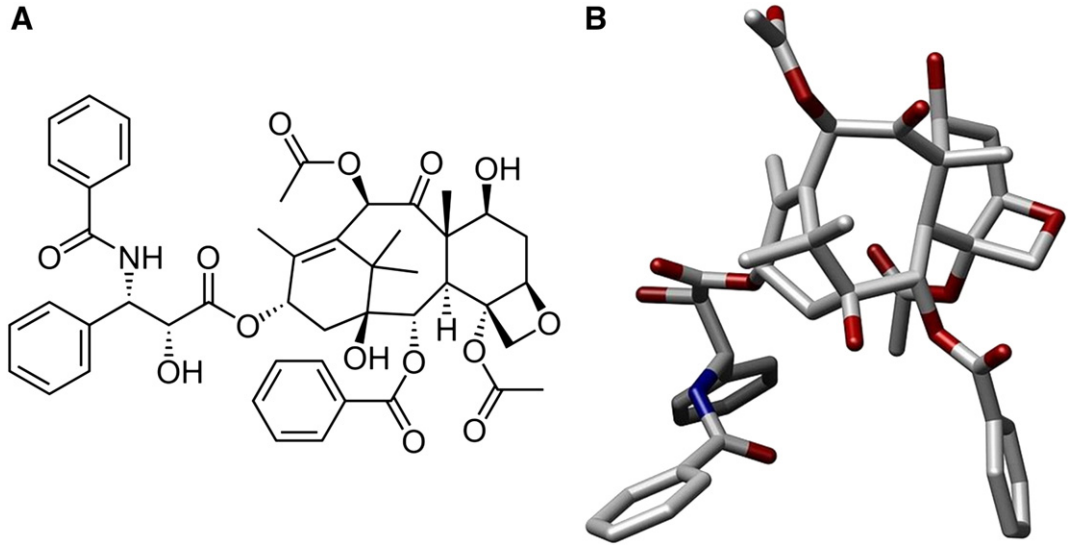

Fig. 1. A) Structural formula of PTX molecule, and B) 3D crystal structure of PTX molecule.