Extended Abstract

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Development of Aqueous Based Formulation of Docetaxel: Safety and Pharmacokinetics in Patients with Advanced Solid Tumors

Ateeq Ahmad1 , Saifuddin Sheikh1 , Shoukath M Ali1 , Moghis U Ahmad1 , Mahesh Paithankar2 , Dipak Saptarishi2 , Kirti Maheshwari2 , Kirushna Kumar3 , Jeba Singh3 , GN Patel4 , Jayanti Patel4 , Ashish Mukhopadhay5 , Ritwik Pandey5 , Chinmoy Bose5 , Singh JK6 , Manisha Singh6 , Rahul Chowdhary6 , Prashant Kale7 and Imran Ahmad1 *

1Jina Pharmaceuticals, Inc. 28100 N. Ashley Ct., Suite 103, Libertyville, IL 60048, USA 2Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat 380009, India 3Meenakshi Mission Hospital and Research Centre, Madurai, Tamil Nadu 625107, India, 4Jeevandeep Hospital, Surat, Gujarat 394210, India , 5Netaji Subhash Chandra Bose Cancer Research Institute, Kolkata, West Bengal 700016, India 6Mahavir Cancer Sansthan, Patna, Bihar 801505, India 7Lambda Therapeutic Research Ltd., Navi Mumbai, Maharashtra 400614, India*Corresponding author: Imran Ahmad, Jina Pharmaceuticals, Inc., 28100 N. Ashley Ct., Suite 103, Libertyville, IL 60048, USA, Tel: 001-847-573-0771; Fax: 001-847-573-0770; E-mail: imran@jinapharma.com

Abstract

A well characterized Nanosomal Docetaxel Lipid Suspension (NDLS) formulation was developed without using any detergent or toxic organic solvents to avoid hypersensitivity reactions caused by the marketed Taxotere® product. The lyophilized NDLS formulation was easily resuspended in water and found to be physically and chemically stable for 48 hours. Physico-chemical characterization of NDLS confirmed a homogeneous formulation with an average particle size of less than 100 nm. Percent Docetaxel association with lipids in NDLS formulation was found to be greater than 95%. The in-vitro release assay showed a sustained release of 25% Docetaxel after 4 hours and 100% Docetaxel release after 42 hours of incubation. Sub-chronic toxicity in mice and rats showed comparable safety to Taxotere®. However, a pharmacokinetics study in rats revealed greater systemic availability of Docetaxel after administration of NDLS compared to Taxotere®. Further, a comparative safety and pharmacokinetic crossover study at 75 mg/m2 of NDLS and Taxotere® in patients with advanced solid tumor also showed higher exposure of Docetaxel with NDLS formulation than patients treated with Taxotere® formulation.

Introduction:

Taxanes are cytotoxic diterpenes used clinically to treat cancer patients. Among the taxanes, the use of Docetaxel is higher due to its enhanced efficacy in most types of cancers especially breast cancer and non-small-cell lung cancer. The enhanced efficacy of Docetaxel is due to its increased potency to stabilize the microtubular assembly and inhibit cell replication [3-5]. Docetaxel is prepared by semi-synthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. It is highly lipophilic and practically insoluble in water. Due to its insolubility, the currently marketed Docetaxel (Taxotere®) is formulated in polysorbate 80 and ethanol. The use of ethanol and polysorbate 80 in Taxotere® formulation causes infusion related toxicities and hypersensitivity reactions in patients. Thus, the patients are pre-medicated with antihistamines and corticosteroids to minimize such toxicities prior to the treatment. However, Taxotere® is still one of the most promising dg approved for the treatment of locally advanced metastatic breast, non-small cell lung, and ovarian cancer. Docetaxel in combination with other drugs is also used for several additional cancer types such as prostate, head and neck and gastric adenocarcinoma [8-10]. To avoid toxicities associated with the excipients such as polysorbate 80/ethanol, and to improve quality of patient's life, a well-characterized Nanosomal Docetaxel Lipid Suspension (NDLS) formulation was developed using Generally Recognized as Safe (GRAS) lipid excipients. The lipid-based drug delivery system has been successfully used for various pharmaceuticals products to provide less toxic drug formulations that result in better quality of life for patients. This may be due to the altered pharmacological distribution and minimal interaction with red blood cells (RBCs) [14]. One of the limitations of all lipid or liposome-based delivery systems is the use of organic solvents to solubilize water insoluble drug and lipids. The organic solvents are removed using standard solvent removal methods to form a thin dry film before hydrating with aqueous medium to prepare lipid or liposome-based preparations. However, the use of organic solvent and its removal process is quite cumbersome and expensive. Therefore, our laboratory is actively engaged in developing organic solvent-free lipid-based drug delivery systems

Conclusion

The development of NDLS, a novel formulation of Docetaxel is described in this report. NDLS was well characterized and found to be stable, safe, and bioavailable. Taken together, NDLS may provide alternate treatment option with enhanced antitumor activity for cancer patients and may not necessitate pre-medication with corticosteroids prior to the treatment. Acknowledgement The toxicological studies in rats and mice were conducted in accordance with CPCSEA at Indian Institute of Toxicology, Pune, India. The LC-MS/MS analysis and pharmacokinetic evaluation were carried out at Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

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