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Author: Yan Wang Shurong Ma Zhongshi Xie Haishan Zhang

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A Synergistic Combination Therapy with Paclitaxel and Doxorubicin Loaded Micellar Nanoparticles

Yan Wang¹, Shurong Ma², Zhongshi Xie³, Haishan Zhang³

¹ Research Center for Gene Therapy, China-Japan Union Hospital, Jilin University, Changchun, China

² Endoscopy Center, China-Japan Union Hospital, Jilin University, Changchun, China

³ Department of Colorectal and Anal Surgery, China-Japan Union Hospital, Jilin University, Changchun, China

Corresponding author: Haishan Zhang, Email: Haishanzhang01@126.com

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Abstract: doxorubicin was chemically conjugated to a biodegradable polymeric carrier as a polymer-doxorubicin (polymer-Dox) conjugate via an acid liable Schiff-base bond. Then, paclitaxel was physically encapsulated by the polymer-Dox conjugate to self assemble in water as micellar nanoparticles with both doxorubicin and paclitaxel in one nanoparticle. In this way, doxorubicin and paclitaxel were combined. The preparation of the polymer-doxorubicin conjugates, encapsulation of paclitaxel, characterization of nanoparticles was systematically studied and the biological evaluation of the free drug combination as well as the micellar platform combination in vitro was thoroughly detailed.

Introduction

Anthracyclines and taxanes are the most effective drugs in the treatment of some solid tumors [1-3]. Anthracyclines demonstrated anticancer effects via forming complexes with DNA and topoisomerase II [4]. Taxanes bind reversibly to β -tubulin to stabilize microtubule complexes and promote microtubule polymerization [5]. Among these, paclitaxel and doxorubicin are most frequently used. The different drug action mechanism provides possibility of combination of the two drugs [6]. Actually, paclitaxel and doxorubicin combination was a favorable and active regimen in the first-line treatment of many solid tumors [1-3]. Moreover, for unresectable cancers, systemic combination chemotherapy is the only option for patients. However, no systemic chemotherapy has been able to provide durable remission. Researchers have shown great promise of the combination of doxorubicin and paclitaxel in hepatocellular carcinoma (HCC) [7,8]. Despite of the progress of combination use of paclitaxel and doxorubicin in cancer therapy, great side effects arises [9,10]. Two phase I studies have shown that administration of a 24-hour paclitaxel infusion prior to doxorubicin results in a significantly higher incidence of mucositis than the reverse sequence [11]. What's more, for combinational use of drug, control of the exact drug concentration and distribution within the tumor microenvironment is one of the most important factors to achieve effective cancer chemotherapy [12-15]. However, it is extremely hard to realize this via small

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