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Co-delivery of vincristine and quercetin by nanocarriers for lymphoma combination chemotherapy

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ABSTRACT

Purpose: Chemotherapy is the current standard treatment for Non-Hodgkin's lymphoma (NHL). Combination therapy is emerging as an important strategy for a better long-term prognosis with decreased side effects, maximized therapeutic effect. The aim of this study is to deliver **vincristine** (VCR) **and quercetin** (QU) with synergistic drug ratios through lipid-polymeric nanocarriers (LPNs) for the lymphoma combination chemotherapy
Methods: In this present study, we constructed VCR and QU dual-loaded LPNs (VCR/QU LPNs) and investigated their antitumor efficacy *in vitro* cell culture models and a tumor xenograft mouse model.
Results: The formulated VCR/QU LPNs exhibited nano-size, negative zeta potential with sustained release profile in vitro. The dual drug loaded LPNs exhibited the best antitumor efficacy *in vitro* and *in vivo*.
Conclusion: It could be concluded that VCR/QU LPNs can combine the efficiency of these two drugs, bring about synergistic effect. Co-encapsulation of VCR and QN in the same LPNs has potential as a novel therapeutic approach to overcome chemo-resistant lymphoma.
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1. Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous grouping of malignant diseases originating in lymph glands and other lymphoid tissue. NHL is the most frequent hematological malignancy; and over the past 3–4 decades, NHL incidence has increased to its current rate of 19.7 new cases per 100,000 people in the US [1,2]. Diffuse large B-cell lymphoma (DLBCL), the most common type of NHL, is responsible for approximately 30–40% of NHL cases in adults [3]. Chemotherapy is the current standard treatment for NHL for both curative and palliative purposes. Cyclophosphamide (CPM), vincristine (VCR), doxorubicin (DOX), and prednisolone (PSL) [CHOP] has been the standard of care for DLBCL [4]. However, relapse, toxicity (myelosuppression), and drug resistance remain a clinical challenge for lymphoma chemotherapy [5]. Therefore, new, tolerable and effective combination treatment approaches are required.

Combination therapy is emerging as an important strategy for a better long-term prognosis with decreased side effects, maximized therapeutic effect [6]. VCR is a widely used antineoplastic agent of the alkaloid class of drugs derived from the periwinkle plant with activity against various types of neoplasms, including leukemia, lymphoma, breast cancer, and lung cancer [7]. VCR also binds to neuronal tubulin, disrupting axonal microtubules and resulting in neurotoxicity, therefore limiting the maximum clinical dose of VCR to 2.0 mg regardless of body surface area [8]. VCR liposome injection (VSLI, Marqibo) is active in advanced NHL and untreated aggressive NHL. The results of phase II study showed that the toxicity profile was manageable with limited hematologic toxicity and might be a component of DLBCL management [9].

Quercetin (3,3′,4′,5,7-penthydroxy flavone, QU), an important polyphenolic bioflavonoid, is found in many fruits and vegetables [10]. Besides antioxidant properties, QU also possesses anticancer and antiviral activities [11]. Recent studies have been reported that QU can inhibit the proliferation of multiple cancer cell lines, including lung, colon, pancreatic, and NHL cells, etc [12–15]. QU exhibited several functions to be an anticancer compound for NHL. These functions include modulation of protein kinase (PKC) signaling and induction of apoptosis through suppression of reactive oxygen species and tumor necrosis factor receptor 1, inhibition of STAT3 pathway, and downregulation of Mcl-1, survivin and p53, etc [15–18]. The cytotoxicity of VCR can be enhanced by QU, which reduced VCR efflux from the cancer cells [19,20]. In view of the low hydrophilicity of VCR and QU, our

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approach is to deliver them with synergistic drug ratios through nanostructured lipid carriers (NLCs).

Nanocarriers such as liposome, polymeric nanoparticles, lipid nanoparticles, micelles have been studied to reduce some side effects of drugs [21–23]. Among them, lipid-polymeric nanocarriers (LPNs) have emerged as a multifunctional drug delivery platform, which combines mechanical advantages of polymeric core and biomimetic advantages of the phospholipid shell into a single platform [24]. Specifically, LPNs exhibit high structural integrity, stability during storage, controlled release, and high biocompatibility and bioavailability owed to the lipid layers [25]. In this present study, we constructed VCR and QU dual-loaded LPNs (VCR/QU LPNs) and investigated their antitumor efficacy *in vitro* cell culture models and a tumor xenograft mouse model.

2. Materials and methods

2.1. Materials

VCR and QU were purchased from Shaanxi Pioneer Biotech Co., Ltd. (Xi'an, China). PLGA (LA:GA = 75:25, Mw ≈ 25,000) was purchased from Jinan Daigang Biomaterial Co, Ltd (Jinan, China). PEG_{2000}-DSPE was provided by was provided by Lipoid GmbH (Ludwigshafen, Germany). Poly (vinyl alcohol) (PVA, 87–89% hydrolyzed, Mw 13,000–23,000), cholesterol, stearic acid, dichloromethane (DCM), and (3-[4,5-dimehyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazolium bromide (MTT) were purchased from Sigma-Aldrich Co., Ltd (St Louis, MO). Roswell Park Memorial Institute (RPMI) 1640 medium and fetal bovine serum (FBS) were obtained from Gibco BRL (Shanghai, China). All other chemicals were of analytical grade or higher.

2.2. Cells and animals

A human Burkitt's lymphoma cell line, Raji cells, was obtained from the American Type Culture Collection (ATCC, Manassas, VA). Cells were cultured in RPMI 1640 medium containing 10% (*v/v*) FBS, 2 mM L-glutamine, 1% (*v/v*) penicillin (100 U/mL) and streptomycin (100 mg/ml) at 37 °C in a 5% CO_2/95% air humidified atmosphere. The vincristine-resistant lymphoma cell line, Raji/VCR cells, was grown in medium containing 0.5 μM VCR for maintaining their drug resistance phenotype.

Male BALB/c mice (6–8 weeks old, 18–22 g weight) were purchased from the Medical Animal Test Center of Shandong Province (Jinan, China), and housed under standard laboratory conditions.

2.3. Preparation of VCR/QU LPNs

VCR/QU LPNs were prepared via the self-assembly of PLGA, cholesterol, stearic acid, and PEG_{2000}-DSPE (with a ratio of 4:2:1:1, *w/w*) using the nanoprecipitation method (Fig. 1) [26]. Briefly, cholesterol (200 mg), stearic acid (100 mg), and PEG_{2000}-DSPE (100 mg) were dissolved in 5% (v/v) ethanol-water solution (30 mL) and warmed to about 60 °C to form solution 1. PLGA (400 mg), VCR (50 mg), and QU (50 mg) were dissolved in acetone (5 mL), and then mixed with 1% PVA water solution (15 mL) to form solution 2. Solution 2 was added dropwise into the solution 1 under stirring at 600 rpm. The resulting dispersion was further stirred until complete evaporation of the organic solvent. Purification was done by washing the nanoparticles dispersion in water three times using an Amicon Ultra-4 centrifugal filter (Millipore Corporation, Bedford, MA). Single drug loaded LPNs (VCR LPNs and QU LPNs) and blank LPNs were prepared in a similar way using one drug (VCR or QU) or no drug. The final formulations were washed three times by repeating centrifugation step and freeze-dried at −20 °C.

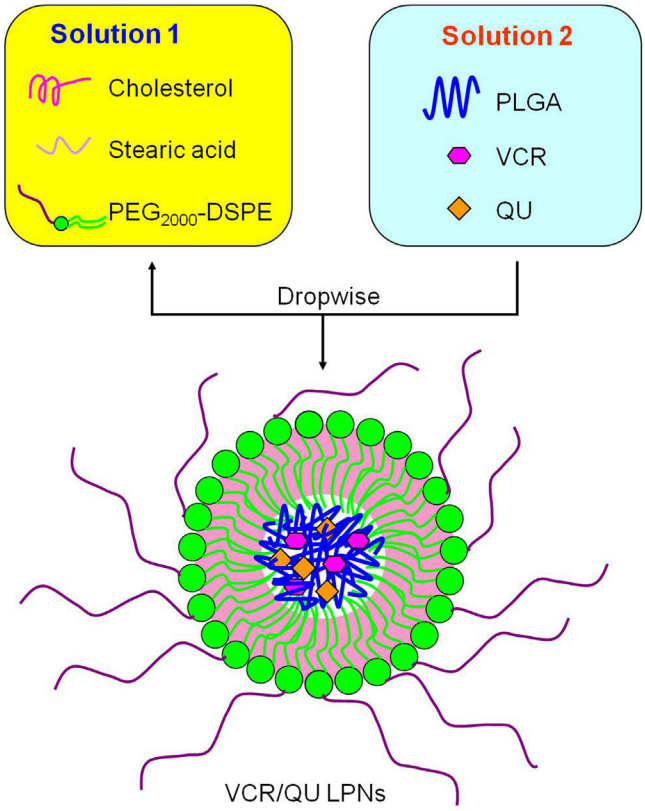

Fig. 1. Preparation of VCR/QU LPNs: VCR/QU LPNs were prepared via the self-assembly of PLGA, cholesterol, stearic acid, and PEG_{2000}-DSPE (with a ratio of 4:2:1:1, *w/w*) using the nanoprecipitation method.

2.4. Characterization of VCR/QU LPNs

The shape and surface morphology of the VCR/QU LPNs were investigated by transmission electron microscopy (TEM, JEOL 1230; JEOL, Tokyo, Japan). The particle size, size distribution (PDI) and zeta potential of VCR/QU LPNs and single drug loaded LPNs were determined by dynamic light scattering (DLS) using a Zetasizer (Nano ZS90, Malvern Instruments Ltd., Malvern, UK) [27]. The average particle size was expressed as volume mean diameter.

VCR loading efficiency (LE) and encapsulation efficiency (EE) was determined by reverse phase high performance liquid chromatography (RP-HPLC) (Shimadzu Co. Ltd., Kyoto, Japan) [28]. Briefly, ethanol was added to disrupt the SLNs or NLCs, and 20 μL of the resulting transparent solution was injected into an HPLC system (Agilent 1260; Agilent Technologies, Santa Clara, CA, USA). A Kromasil C18 reverse phase column (150 × 4.6 mm, 5 μm; AkzoNobel, Separation Products, Bohus, Sweden) and the mobile phase consisting of acetonitrile and 0.01 M NaH_2PO_4 (55/45, v/v, pH 7.0 adjusted with triethylamine) were used to separate the targeted component. The samples were eluted by mobile phase at a flow rate of 1.0 mL/min at 35 °C and monitored at 297 nm.

The QU LE and EE were determined by a spectrophotometer (UV-2102, Shanghai Instrument Co., Ltd, Shanghai, China) with the detection wavelength at 373 nm [10]. Free QU in LPNs was separated using ultrafiltration. This was carried out using a filter membrane with molecular weight cut-off (MWCO) of 100,000. A certain volume of LPNs suspension was accurately taken, dissolved and diluted with absolute alcohol. The resulting solution was determined with UV–vis at 373 nm and the total amount of QU was obtained. The same volume of LPNs suspension was accurately taken and ultrafiltered, then the ultrafiltrate was diluted with absolute alcohol and the resulting solution was determined under

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