Chiu et al. BMC Cancer (2015) 15:962
DOI 10.1186/s12885-015-1970-x

BMC Cancer

RESEARCH ARTICLE Open Access

BPIQ, a novel synthetic quinoline derivative, inhibits growth and induces mitochondrial apoptosis of lung cancer cells *in vitro* and *in zebrafish xenograft model*

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Abstract

Background: 2,9-Bis[2-(pyrrolidin-1-yl)ethoxy]-6-{4-[2-(pyrrolidin-1-yl)ethoxy] phenyl}-11*H*-indeno[1,2-*c*]quinolin-11-one (BPIQ) is a derivative from 6-arylindeno[1,2-*c*]quinoline. Our previous study showed the anti-cancer potential of BPIQ compared to its two analogues topotecan and irinotecan. In the study, the aim is to investigate the potency and the mechanism of BPIQ against lung cancer cells.

Methods: Both *in vitro* and zebrafish xenograft model were performed to examine the anti-lung cancer effect of BPIQ. Flow cytometer-based assays were performed for detecting apoptosis and cell cycle distribution. Western blot assay was used for detecting the changes of apoptotic and cell cycle-associated proteins. siRNA knockdown assay was performed for confirming the apoptotic role of Bim.

Results: Both *in vitro* and zebrafish xenograft model demonstrated the anti-lung cancer effect of BPIQ. BPIQ-induced proliferative inhibition of H1299 cells was achieved through the induction of G_2/M-phase arrest and apoptosis. The results of Western blot showed that BPIQ-induced G_2/M-phase arrest was associated with a marked decrease in the protein levels of cyclin B and cyclin-dependent kinase 1 (CDK1). The up-regulation of pro-apoptotic Bad, Bim and down-regulation of pro-survival XIAP and survivin was observed following BPIQ treatment.

Conclusions: BPIQ-induced anti-lung cancer is involved in mitochondrial apoptosis. BPIQ could be a promising anti-lung cancer drug for further applications.

Keywords: Indeno[1,2-*c*]quinolinequinoline, BPIQ, Lung cancer, Apoptosis, Polyploidy, Zebrafish xenograft

Background

Lung cancer is one of the leading malignancies worldwide, and non-small cell lung cancer (NSCLC) accounts for at least 80 % of lung cancer [1]. Approximately one out of three patients with NSCLC has locally advanced disease that is surgically unavailable [2]. Nowadays, chemotherapeutic strategies for NSCLC therapy are constantly developed and improved [2–6]. However, the poor prognosis at an advanced stage of NSCLC and chemotherapeutic resistance contribute to the low survival rate of NSCLC patients [3].

Quinoline ring was found in a variety of biologically active compounds, which exert the anti-inflammation [7], anti-autoimmunity [8] and anti-cancer proliferative activities [7, 9–12]. The well-known quinoline derivative, camptothecin (CPT) is a pentacyclic quinoline isolated from the Chinese tree *Camptotheca acuminata*, which was reported to possess a potent cytotoxicity in a variety of cancers (Fig. 1a). CPT derivatives including irinotecan and topotecan are widely used as anti-cancer drugs [11]. However, the inherent chemical properties of CPT, including poor solubility and instability under physiological conditions, prevent its full clinical applications [13].

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