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Original Article

Synergistic Effect of Docetaxel Combined with Quinacrine on Induction of Apoptosis and Reduction of Cell proliferation in a Lung Cancer Cell Line

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ABSTRACT

Background and objectives: Combination chemotherapy with new adjuvants has been introduced as an innovative method of treating various types of cancer. The aim of this study was to investigate potential synergistic effect of quinacrine on the anti-proliferative and anti-apoptotic activity of docetaxel in A549 lung cancer cells.

Methods: Cell viability and apoptosis percentage were evaluated with MTT assay and annexin V staining. To understand the mechanisms through which quinacrine modulates expression of pro-apoptotic and anti-apoptotic genes, expression of Bcl-2, Bcl-xl and Bax genes were investigated using real-time RT-PCR.

Results: The half maximal inhibitory concentration values for docetaxel and quinacrine was 3.16±1.5 nM and 4.4±0.58 μ M, respectively. The combination index value of docetaxel and quinacrine was 0.66 against A549 cells, indicating strong synergism. The expression of anti-apoptotic genes Bcl-2 and Bcl-xl reduced significantly, while the expression of the pro-apoptotic gene Bax increased significantly after co-treatment with docetaxel and quinacrine ($P<0.05$). Treatment of cells with a combination of quinacrine and docetaxel significantly increased the inhibitory effect of docetaxel (reduced proliferation by 50%) and the percentage of apoptotic cells.

Conclusion: Our findings suggest that the combination of quinacrine and docetaxel can be considered as a promising strategy for the treatment of patients with lung cancer.

Keywords: Quinacrine, Apoptosis, Docetaxel, Cell Proliferation.

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INTRODUCTION

Lung cancer is the main cause of cancer death worldwide (1, 2). Over the last decade, several strategies such as daily screening, early detection and new alternative treatments have been developed to improve survival of cancer patients (3). Currently, the best treatment options for cancer are surgery, radiation therapy and chemotherapy. Chemotherapy is the most commonly used method of treating solid tumors, particularly in patients with metastatic cancer (4).

Docetaxel is widely used as a first-line therapy for patients with lung cancer (5, 6). The drug attaches to beta-tubulin subunit of microtubules, thereby causing cell apoptosis (7). However, docetaxel causes a number of unwanted side effects, including gastrointestinal toxicity, hypersensitivity and neurotoxicity (8). Combination therapy with new anticancer drugs and chemotherapeutics is a promising approach to overcome the side effects of chemotherapy. It has been shown that the growth, survival, invasion and metastasis of cancer cells are driven by more than one signaling pathway; therefore, the combination of chemotherapy drugs and new anti-cancer agents may help inhibit multiple signaling pathways involved in cancer progression (9).

The constitutive activation of NF-κB transcription factor has been identified in a number of human malignancies, including multiple myeloma, breast, head and neck, colon, prostate and lung cancers (10). The activated NF-κB transcription factor has been shown to be associated with cancer cell stimulation, apoptotic inhibition and increased angiogenic and metastatic potential of tumors. The activation of NF-κB/Rel plays an important role in inflammation by inducing transcription of several pro-inflammatory genes (11). This transcription factor also activates several target genes that stop the induction of apoptosis by TNF-α and other pro-apoptotic factors. The anti-apoptotic agents induced by NF-κB include cIAPs, caspase-8/FADD, and Bcl-2 family members (such as A1/BFL1 and Bcl-xl). This protein can also reduce apoptotic responses to genotoxic anticancer drugs and ionization radiation. Tumor cells in which NF-κB is constitutively active are highly resistant to anticancer drugs or ionizing radiation, and inhibition of NF-κB activity in these cells increases their sensitivity to such treatments (12-14).

A recent screening of a compound called 9-aminoacridine also includes quinacrine, has been identified as a p53 activator and NF-kB inhibitor (15). The mechanism of action of quinacrine appears to be intercalating in the DNA through the planar acridine ring, while the secondary chain of diaminobutyl is inserted into the small groove of DNA. A recent study has shown that quinacrine and its derivatives can inhibit NF-κB (16). In this study, we aimed to investigate the potential synergistic effect of combination therapy using docetaxel and quinacrein against lung cancer cells.

MATERIAL AND METHODS

Human lung cancer cells (A549) were obtained from the Pasteur Institute of Iran (Tehran, Iran). The cells were cultured in RPMI-1640 medium (Gibco; Thermo Fisher Scientific, Inc ,Waltham, MA, USA) containing 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc, Waltham, MA, USA) and 100 U/ml streptomycin/penicillin (Sigma Aldrich Merck KGaA , Darmstadt, Germany) at 37 ° C for 24 hours in a 5% CO2 atmosphere. The cells were cultured onto a 96-well plate containing 4,000 cells per well. After 24 hours, the cells were treated with different concentrations of quinacrine (0-50 μM) and docetaxel (0-16 nM) for 24, 48 and 72 hours. Later, the medium was replaced with 200 μl of fresh medium containing 20 μl MTT (2 mg/ml) and the plate was incubated for four hours at 37 °C. Next, the content of

the wells was removed and replaced with 200 µl of dimethyl sulfoxide + 25 µl of glycine Sorenson buffer (17). The absorbance was measured at 570 nm using the Awareness Technology stat fax 3200 microplate reader (Awareness Technology Inc., Palm City, FL, USA). The half-maximal inhibitory concentration (IC50) was calculated using the GraphPad Prism 6.0 software.Combined analysis was carried out to determine the effects of combination therapy with quinacrine and docetaxel on A549 cells using the Chou and Talalay's method (18). Compound 1 (quinacrine) had a constant concentration (2.5 µM) while compound 2 (docetaxel) was prepared in different concentration (1, 2, 3 and 5 nM).

Synergic effects of the two agents were evaluated using CI method and isobologram. This technique relies on the theory of median effect, in which the isobologram analysis and drug interactions are characterized by the CI (19). A CI of less than, equal to and more than 1 indicates synergy, additively and antagonism, respectively.

Apoptosis was evaluated using the annexin V-FITC apoptotic detection kit. For this purpose, the cells were seeded on a 6-well plate (3×105 cells/well) and treated with docetaxel (2 nM), quinacrine (2.5 µM) or their combination for 24 hours. The cells were harvested from the plate and washed with phosphate buffer saline and then suspended in the binding buffer and stained with annexin V and propidium iodide (20). Flow cytometry analysis was performed using BD FACSCalibur ™ (BD Biosciences, Franklin Lakes, NJ, USA) and the FlowJo software (FlowJo LLC, Ashland, OR, USA).

Total RNA was extracted using the TRI Reagent solution (Sigma-Aldrich) based on the manufacturer's instructions (21). The amount of extracted RNA was measured using NanoDrop 1000 (Thermo Fisher Scientific). Then, 1 µg of RNA from each sample was used to generate cDNA using the Reverse Aid Reverse Transcriptase Kit. Relative expression of the genes was determined using Cyber Green master mix and a Roche LightCycler (Switzerland). The primer sequences used for each gene are presented in Table 1.

Data are presented as mean ± standard deviation. Moreover, IC50 values were calculated using GraphPad software (version 6) and nonlinear repression analysis. The paired t-tests and one-way analysis of variance with Tukey's range test were performed to investigate variations. A P-value of less than 0.05 was considered as statistically significant.

Table 1. The primer sequence of genes

Gene	Primer sequence
Bcl-2	Forward: 5’-CATCAGGAAGGCTAGAGTTACC-3’
	Reverse: 5’-CAGACATTCGGAGACCACAC-3’
BAX	Forward: 5’-GATGCGTCCACCAAGAAG-3’
	5’-AGTTGAAGTTGCCGTCAG-3’ Reverse:
Bcl-xl	Forward: 5’- TCCTTGTCTACGCTTTCCACG-3’
	5’-GGTCGCATTGTGGCCTTT-3’ Reverse:
β-actin	Forward: 5’-TGCCCATCTACGAGGGGTATG-3’
	Reverse: 5’-CTCCTTAATGTCACGCACGATTTC-3’

RESULTS

The anti-proliferative effects of docetaxel and quinacrine on A549 cells

The anti-proliferative activity of docetaxel and quinacrine on A549 cells was measured using MTT assay. Docetaxel and quinacrine showed dose-dependent cytotoxic effects against A549 cells (Figure 1). Docetaxel potently inhibited the proliferation of A549 cells with IC50 of 3.61 ± 1.5 nM (Figure 1A), increasing drug concentration and incubation time, as well as increasing the anti-proliferative effects of docetaxel and quinacrine on cells.

In order to evaluate whether quinacrine reduces cytotoxic effects of docetaxel, the inhibitory effects of these compounds on A549 cells were assessed alone and combined. The cells were treated with 2.5mM quinacrine and different concentrations (1, 2, 3 and 5 nM) of docetaxel for 24 hours. Co-treatment of A549 cells cells with 2 nM of docetaxel and 2.5 µM of quinacrine significantly decreased cell viability compared with docetaxel (Figures A and B). The isobologram curves showed a strong synergistic effect between the two agents (Figure 2B). A CI value of 0.64 was achieved after co-treatment of cells with 2.5 µM quinacrine and 2 nM docetaxel, which indicates strong synergism.

The proportion of apoptotic cells was calculated by annexin V and PI staining using flow cytometry analysis. The results showed that combined treatment of cells with quinacrine and docetaxel significantly increased apoptosis in the cell population when compared with single treatment. Docetaxel alone increased the number of early apoptotic A549 cells by 35.9%. Combined treatment increased the population of early apoptotic cells from 35.9% to 61.66%, compared to single treatment.

The expression of the main pro- and anti-apoptotic genes was determined using RT-qPCR following incubation of cells with 2.5 µM quinacrine and 2 nM docetaxel. The results showed that the co-treatment significantly reduced expression of Bcl-2 and Bcl-xl compared to single treatment. The expression of Bax increased significantly after treatment with quinacrine and docetaxel alone (P=0.021) or combined (P =0.011). These results showed that quinacrine can regulate the expression of key apoptosis-related genes (Figure 3).

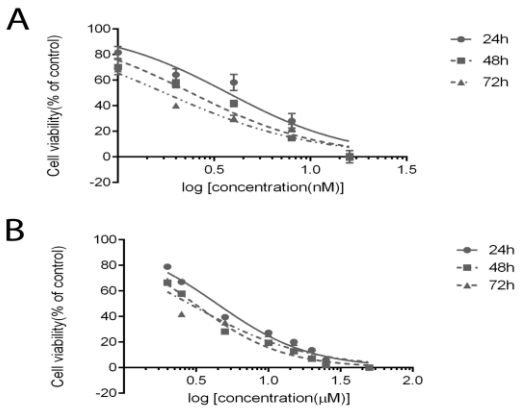

Figure 1. Anti-proliferative effects of quinacrine (A) and docetaxel (B) on A549 cells after 24, 48 and 72 hours.

Data are representative of three individual experiments (n=3).

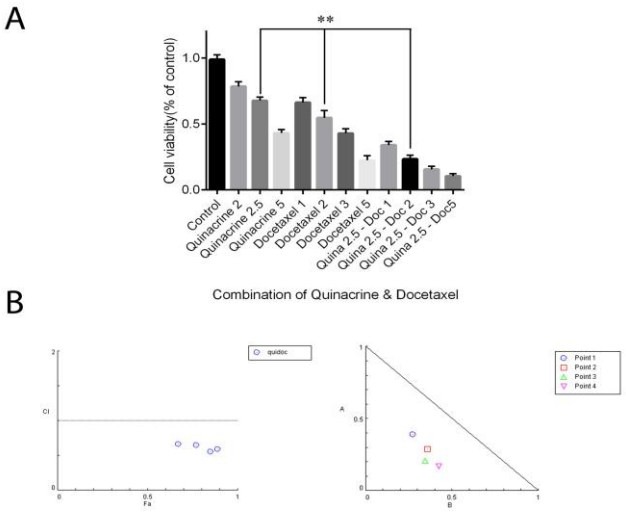

Figure 2. The inhibitory effects of quinacrine combined with docetaxel on viability of A549 cells. (A) Cell viability after treatment of cells with different concentrations (1,2,3 and 5 nM) of docetaxel, quinacrine (2,2.5 and 5 mM) and the combination of the two drugs for 24 hours. (B) CI and normalized isobolograms of docetaxel-quinacrine on A549 cells. Data are representative of three individual experiments (n=3). CI values <1 indicate synergism. **P < 0.01.

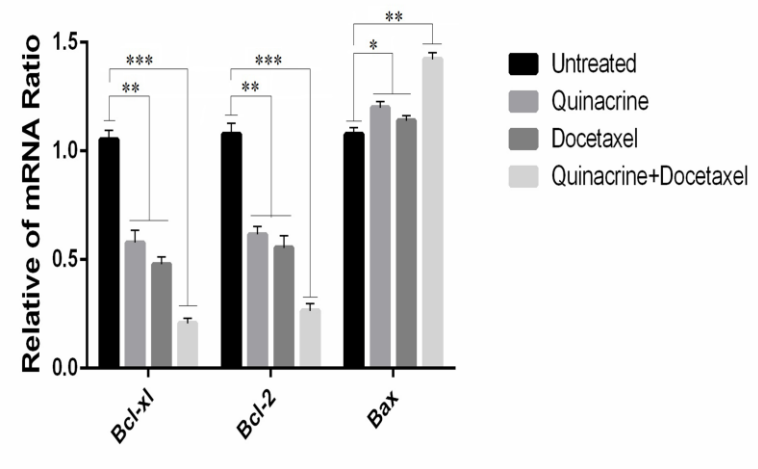

Figure 3. Effect of quinacrine, docetaxel and their combination on expression of Bcl-xl, Bcl-2 and BAX in A549 cells. The results are presented as the mean ± standard deviation of three independent experiments. Bax mRNA expression: *P < 0.05 single treatment vs. control; Bcl-xl and Bcl-2 mRNA expression: **P < 0.01 single treatment vs. control; Bcl-xl and Bcl-2 mRNA expression: ***P < 0.001 combined treatment vs. control.

DISCUSSION

Docetaxel is a common chemotherapeutic drug used for treatment of lung cancer (22). Currently, a combination of two or more agents is utilized for treatment of diseases. Combination chemotherapy may increase the effectiveness of chemotherapeutic agents, reduce cellular toxicity in the host and reduce drug resistance (23). NF-κB inhibitors are recommended for increasing the anticancer effects of current chemotherapeutic regimens (24, 25). Combination therapy with conventional chemotherapeutics and quinacrine can overcome the side effects associated with chemotherapy. In the present study, quinacrine was able to increase the anticancer effects of docetaxel on a lung cancer cell line, in which NF-κB is constitutively active.

NF-κB regulates the expression of anti-inflammatory and anti-apoptotic proteins (26). It has been showed that inhibiting NF-κB in lymphoid cells results in downregulation of some Bcl-2-associated proteins. This might indicate that some of these factors may be downstream of the NF-κB in the survival cascade (27).

It has been demonstrated that the Bcl-2 counterpart is widely controlled by Rel/NF-κB, which is consistent with these results (28). Therefore, it is important to determine whether NF-κB is a general or specific apoptosis antagonist. There is a strong correlation between anti-apoptotic activity and oncogenic activity of the NF-κB. Extensive search has been done on genes involved in the NF-κB survival pathway. A recent study by Hettmann et al. showed that NF-κB directly regulates the expression of Bcl-2, Bfl-1 and its homologous A1 protein (28). It has been demonstrated that Bcl-xl is also a transcription target of NF-κB (28).

Several in vitro and in vivo studies have been conducted to evaluate effects of combination therapy using quinacrine and chemotherapeutic agents on growth, cell cycle regulation and apoptosis (29). Khurana et al. reported that quinacrine significantly increases the cytotoxicity of cisplatin in a dose-dependent pattern, indicating that quinacrine could be used as a potential chemotherapy adjuvant when combined with cisplatin. In the mentioned study, the combination of quinacrine and cisplatin significantly reduced expression of cIAP-1 and significantly overexpressed Bax (30).

Finally, quinacrine increases the effectiveness of chemotherapy drugs such as adriamycin, 5-FC, etoposide, CPT11, sorafenib, and gemcitabine, and carcinoma cells kill hepatocellular cells in vitro. In a study by Wang et al., the combination of quinacrine and surfenib (sorefnib) can effectively eliminate Mcl-1 and increase sensitivity of HepG2 cells to TRAIL, indicating that quinacrine may increase the efficacy of chemotherapy drugs such as adriamycin, 5-FC, etoposide, CPT11, sorafenib and gemcitabine (31).

In the present study, we evaluated effect of co-treatment with quinacrine and docetaxel on viability of A549 cancer cells. The results showed that combination of docetaxel (2 nM) and quinacrine (2.5 μM) could significantly increase the inhibitory activity of docetaxel from 46% to 74%. In addition, the CI calculation with the CompuSyn software showed that the CI for the two aforementioned agents was 0.66 against A549 cells, which indicates synergism. Therefore, it can be concluded that the combination of docetaxel with quinacrine can enhance the effectiveness of docetaxel in inhibiting the growth of A549 cancer cells. It is well demonstrated that κB regulates the expression of many genes critical for cell survival. This transcription factor is activated by various stimuli such as proinflammatory cytokines, cellular stress and growth factors. On the other hand, its activation is strongly regulated by inhibitor of κB (IκB). Phosphorylation of this protein

leads to its proteinase degradation, thus allowing active transfer of NF-κB to the nucleus where it can initiate transcription of survival-related genes (32). In this way, the activation of NF-κB results in increased expression of apoptotic inhibitors, survivin, Bcl-2 and Bcl-xl. Continuous activation of NF-κB has been identified in several types of cancer, including colorectal cancer, prostate cancer, pancreatic cancer, lung cancer, neuroblastoma, T-cell leukemia, multiple myeloma and breast cancer (33). Increased NF-κB activity leads to overexpression of anti-apoptotic factors, such as Bcl-xl, Bcl-2, Mcl-1 and survinin.

CONCLUSION

The results of this study show that quinacrine, as a NF-κB inhibitor, increases the cytoxicity of docetaxel on A549 cells. The synergistic anti-cancer effects of quinacrine and docetaxel seem to be associated with the Bcl-2 and Bcl-xl downexpression. These results suggest that the use of NF-κB inhibitors along with taxane derivatives may be a promising approach for treatment of patients with lung cancer.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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