Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
We have previously demonstrated that non-small cell lung cancer cell, H460, had strong drug resistance to TGFβ and can grow and metastasize successfully in animal model. Despite the fact TGFβ can suppress the growth of gastric carcinoma and hepatoma cells, it also promotes the epithelial mesenchymal transition (EMT) and/or metastasis of liver and breast cancers. We therefore were interested to know would TGFβ also promote the EMT and triggered signaling pathway, TGFβ/ERK, and breast cancers. We therefore were interested to know would the growth of gastric carcinoma and hepatoma cells, it also promotes.

Results: Among the derivatives, Compound3 showed the most potent effect on cancer cells and induction of monoastral formation. The efficacy of Plumbagin in vivo was evaluated with intraperitoneal injection of plumbagin (2 mg/kg body weight) daily for three weeks using subcutaneous NB4 xenograft in NOD/SCID mice, comparing with the vehicle and Doxorubicin (1 mg/kg thrice a week). The tissue sections were applied to hematoxylin and eosin histological staining as well as TUNEL assay.

Conclusions: We revealed that plumbagin triggered the mitochondrial apoptotic pathway, as indicated by the increase in Bax/Bcl-2 ratios, resulting in a reduction of mitochondrial membrane potential and corresponding caspase activation. We also found that the generation of ROS was a critical mediator in plumbagin-induced cell apoptosis, which would be abrogated completely by the antioxidant, NAC. Furthermore, compared with the control, Plumbagin presented a >60% reduction in tumor volume and marked increase in tumor apoptosis; There was no overt manifestation of toxicity such as weight loss, tissue damage and behavior change as showed in Doxorubicin -treated mice.

Conclusion: Our data support that Plumbagin has potential as a novel therapeutic agent for myeloid leukemia with minimal side-effects.

Conclusions: It is suggested that Compound3 should be considered for further exploration and development and that induction of monoastral formation may not work as a predictive biomarker. Taken together, a novel mitotic kinesin Eg5 inhibitor Compound3 may have other mechanisms of action for its growth inhibitory effect on cancer cells and further investigation on alternative biomarkers is necessary to develop Eg5 inhibitors as an anticancer drug.

A novel mitotic kinesin Eg5 inhibitor exerts the growth inhibitory effect on cancer cells in a manner independent of either Eg5 expression level nor induction of monoastral formation.

Background: Mitotic kinesin Eg5 plays an important role in mitosis, as it is critical for proper bipolar spindle assembly. After the discovery of the first Eg5 inhibitor monastrol, a number of Eg5 inhibitors have been developed as anticancer drugs. We have synthesized a series of S-trityl-L-cysteine (STLC) derivatives as Eg5 inhibitors and showed potent growth inhibitory effect on cancer cells and induction of monoastral formation. Small molecule and cell line studies indicate that STLC-based inhibitors are well-tolerated and exhibit antiproliferative activity in a range of tumor cell lines.

Materials and Methods: Growth inhibitory effects of monastrol and STLC derivatives, Compound1, Compound2 and Compound3 were evaluated by MTT assay in MKN1, MKN45, MKN74, NUGC3, NUGC4, NCI-N87 gastric cancer cell lines, C170, DLD1, HCT15, COLO205 colon cancer cell lines and AsPC1, BxPC3, SUIT2 pancreatic cancer cell lines. Cell cycle analysis and immunocytochemistry were carried out to evaluate the induction of mitotic arrest and monoastral formation, respectively. Expression levels of Eg5, BubR1 and MAD2 were evaluated by western blot for a predictive biomarker study.

Results: Among the derivatives, Compound3 showed the most potent growth inhibitory effect with IC50 ranging from 0.16 to 0.89 μM except for AsPC3 cells, while monastrol showed almost no effect at concentrations up to 10 μM. Compound3 induced G2/M arrest as early as 8 hours after the treatment at a concentration of IC50. Induction of monoastral formation was modestly observed in BxPC3 and HCT15 cells which are sensitive to Compound3, while it was also observed in AsPC3 cells which are not sensitive to Compound3 with an IC50 of around 10 μM. There was no correlation observed between the growth inhibitory effect and the Eg5 expression level and no significant change was observed in the BubR1 or MAD2 expression level after the treatment, either.

Materials and Methods: In order to elucidate the molecular mechanism involved in plumbagin-induced apoptosis, we studied the effect of Plumbagin with IC50 (9 μM) by monitoring the activity of the caspase-3 and caspase-9, the change of mitochondrial membrane potential (ΔΨm), the expression of the Bcl-2 family as well as ROS change in plumbagin-induced apoptosis. The efficacy of Plumbagin was further evaluated with intraperitoneal injection of plumbagin (2 mg/kg body weight) daily for three days using subcutaneous NB4 xenograft in NOD/SCID mice, comparing with the vehicle and Doxorubicin (1 mg/kg thrice a week). The tissue sections were applied to hematoxylin and eosin histological staining as well as TUNEL assay.

Conclusion: We found that plumbagin triggered the mitochondrial apoptotic pathway, as indicated by the increase in Bax/Bcl-2 ratios, resulting in a reduction of mitochondrial membrane potential and corresponding caspase activation. We also found that the generation of ROS was a critical mediator in plumbagin-induced cell apoptosis, which would be abrogated completely by the antioxidant, NAC. Furthermore, compared with the control, Plumbagin presented a >60% reduction in tumor volume and marked increase in tumor apoptosis; There was no overt manifestation of toxicity such as weight loss, tissue damage and behavior change as showed in Doxorubicin -treated mice.

Conclusion: Our data support that Plumbagin has potential as a novel therapeutic agent for myeloid leukemia with minimal side-effects.

Artemisinin derivatives are well-tolerated anti-malaria drugs that also exert anti-cancer activity. Here, we investigated artemisinin and its derivatives dihydroartemisinin and artesunate in a panel of chemoresistant neuroblastoma cell lines.

Artemisinin and its derivatives are effective in vitro against a panel of primary cell lines from neuroblastoma, at least two primary culture lines, only UKF-NB-3′DCCPP showed low sensitivity to artesunate. Artesunate induced apoptosis and reactive oxygen species in neuroblastoma cells. L-Buthionine-S,R-sulfoximine, an inhibitor of GCL (glutamate-cysteine ligase), resensitised in part UKF-NB-3′DCCPP cells to artesunate. This finding together with bioinformatic analysis of gene microarray data was used to identify genes relevant for neuroblastoma cell response to artesunate. Results: Only dihydroartemisinin and artesunate affected neuroblastoma cell viability with artesunate being more active. Of 16 cell lines and two primary cultures, only UKF-NB-3′DCCPP showed low sensitivity to artesunate. Artesunate induced apoptosis and reactive oxygen species in neuroblastoma cells. L-Buthionine-S,R-sulfoximine, an inhibitor of GCL (glutamate-cysteine ligase), resensitised in part UKF-NB-3′DCCPP cells to artesunate. This finding together with bioinformatic analysis of gene microarray data was used to identify genes relevant for neuroblastoma cell response to artesunate.

Results: Cell viability was determined by MTT assay or by determination of ATPase activity. Apoptosis was examined by staining for activated caspase-3 and detection of cells with low DNA content (sub-G1) by flow cytometry. Bioinformatic analysis of gene microarray data was used to identify genes relevant for neuroblastoma cell response to artesunate.