



Letter to the Editor:

Artesunate and its emerging anti-neoplastic effects: beyond its role in attenuating tumor growth in osteosarcomas

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I read with great interest the recent article “Artesunate inhibits growth and induces apoptosis in human osteosarcoma HOS cell line in vitro and in vivo” by Xu *et al.* (2011), published in *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*. Artesunate exerts anti-neoplastic effects in a number of systemic malignancies besides osteosarcomas.

Artesunate exerts anti-proliferative effects in pulmonary adenocarcinomas. It mediates these anti-neoplastic effects by virtue of activating Bak (Zhou *et al.*, 2012). At the same time, it down-regulates epidermal growth factor receptor expression. This results in augmented non-caspase dependent apoptosis in the adenocarcinoma cells. Artesunate mediated apoptosis is time as well as dose dependent. Interestingly, AIF and Bim play significant roles in this Bak-dependent accentuated apoptosis (Ma *et al.*, 2011). Adenosine triphosphate (ATP)-binding cassette subfamily G member 2 (ABCG2) expression is also attenuated while transcription of matrix metalloproteinase 7 (MMP-7) is also down-regulated (Zhao *et al.*, 2011). In addition, artesunate enhances the radiosensitization of lung carcinoma cells. It mediates this effect by down-regulating cyclin B1 expression, resulting in augmented G₂/M phase arrest (Rasheed *et*

al., 2010).

Similarly, artesunate exhibits anti-neoplastic effects in breast carcinomas. Artesunate administration is typically accompanied by attenuated turnover as well as accentuated peri-nuclear localization of autophagosomes in the breast carcinoma cells. Mitochondrial outer membrane permeability is typically augmented. As a result, artesunate augments programmed cellular decline in breast carcinoma cells (Hamacher-Brady *et al.*, 2011). Lysosomal iron plays a major role in the production of reactive oxygen species (ROS). Similarly, artesunate inhibits the PI3K/Akt signaling pathway in cervical malignancies. The expression of Bcl-xL is markedly attenuated. As a result, it accentuates tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced intrinsic as well as extrinsic apoptosis in these cancers (Thanaketspaisarn *et al.*, 2011). It also decreases TRAIL induced nuclear factor- κ B (NF- κ B) activity.

Artesunate also exerts anti-neoplastic effects in skin malignancies. It mediates these effects by up-regulating p21. At the same time it down-regulates cyclin D1 (Jiang *et al.*, 2012). Cdk4 is also down-regulated simultaneously. As a consequence there is accentuated G₀/G₁ phase arrest. Artesunate also augments iron-dependent mitochondrial apoptosis. Similarly, artesunate enhances the radiosensitivity of tumors such as gliomas. It mediates this effect by down-regulating the expression of surviving (Reichert *et al.*, 2012). As a result, there is increased G₂/M phase arrest. Intra-tumoral apoptosis is also markedly accentuated.

The above examples clearly illustrate the significant anti-proliferative and apoptosis enhancing effects of artesunate and the need for further large scale studies in this regard.

References

- Hamacher-Brady, A., Stein, H.A., Turschner, S., Toegel, I., Mora, R., Jennewein, N., Efferth, T., Eils, R., Brady, N.R., 2011. Artesunate activates mitochondrial apoptosis in breast cancer cells via iron-catalyzed lysosomal reactive oxygen species production. *J. Biol. Chem.*, **286**(8): 6587-6601. [doi:10.1074/jbc.M110.210047]
- Jiang, Z., Chai, J., Chuang, H.H., Li, S., Wang, T., Cheng, Y., Chen, W., Zhou, D., 2012. Artesunate induces G₀/G₁ cell cycle arrest and iron-mediated mitochondrial apoptosis in A431 human epidermoid carcinoma cells. *Anticancer Drugs*, **23**(6):606-613. [doi:10.1097/CAD.0b013e328350e8ac]
- Ma, H., Yao, Q., Zhang, A.M., Lin, S., Wang, X.X., Wu, L., Sun, J.G., Chen, Z.T., 2011. The effects of artesunate on the expression of EGFR and ABCG2 in A549 human lung cancer cells and a xenograft model. *Molecules*, **16**(12):10556-10569. [doi:10.3390/molecules161210556]
- Rasheed, S.A., Efferth, T., Asangani, I.A., Allgayer, H., 2010. First evidence that the antimalarial drug artesunate inhibits invasion and in vivo metastasis in lung cancer by targeting essential extracellular proteases. *Int. J. Cancer*, **127**(6):1475-1485. [doi:10.1002/ijc.25315]
- Reichert, S., Reinboldt, V., Hehlhans, S., Efferth, T., Rodel, C., Rodel, F., 2012. A radiosensitizing effect of artesunate in glioblastoma cells is associated with a diminished expression of the inhibitor of apoptosis protein survivin. *Radiother. Oncol.*, **103**(3):394-401. [doi:10.1016/j.radonc.2012.03.018]
- Thanaketpaisarn, O., Waiwut, P., Sakurai, H., Saiki, I., 2011. Artesunate enhances TRAIL-induced apoptosis in human cervical carcinoma cells through inhibition of the NF-kappaB and PI3K/Akt signaling pathways. *Int. J. Oncol.*, **39**(1):279-285. [doi:10.3892/ijo.2011.1017]
- Xu, Q., Li, Z.X., Peng, H.Q., Sun, Z.W., Cheng, R.L., Ye, Z.M., Li, W.X., 2011. Artesunate inhibits growth and induces apoptosis in human osteosarcoma HOS cell line in vitro and in vivo. *J. Zhejiang Univ-Sci. B (Biomed. & Biotechnol.)*, **12**(4):247-255. [doi:10.1631/jzus.B1000373]
- Zhao, Y., Jiang, W., Li, B., Yao, Q., Dong, J., Cen, Y., Pan, X., Li, J., Zheng, J., Pang, X., *et al.*, 2011. Artesunate enhances radiosensitivity of human non-small cell lung cancer A549 cells via increasing no production to induce cell cycle arrest at G₂/M phase. *Int. Immunopharmacol.*, **11**(12):2039-2046. [doi:10.1016/j.intimp.2011.08.017]
- Zhou, C., Pan, W., Wang, X.P., Chen, T.S., 2012. Artesunate induces apoptosis via a bak-mediated caspase-independent intrinsic pathway in human lung adenocarcinoma cells. *J. Cell Physiol.*, **227**(12):3778-3786. [doi:10.1002/jcp.24086]

Recommended paper related to this topic

Artesunate inhibits growth and induces apoptosis in human osteosarcoma HOS cell line in vitro and in vivo

Authors: Qiang XU, Zhao-xu LI, Hui-qin PENG, Zheng-wang SUN, Rui-lin CHENG, Zhao-ming YE, Wei-xu LI

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Abstract: This paper aims to investigate the effects of artesunate (ART) on growth and apoptosis in human osteosarcoma HOS cell line in vitro and in vivo and to explore the possible underlying mechanisms. Cell viability was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The induction of apoptosis was detected by light and transmission electron microscopy and flow cytometry. Western blot analysis was used to investigate the related mechanisms. Nude mice were further employed to investigate the antitumour activity of ART in vivo. MTT assay results demonstrated that ART selectively inhibits the growth of HOS cells in a dose- and time-dependent manner. Based on the findings of light and transmission electron microscopy, Hoechst 33258 staining, and fluorescein isothiocyanate (FITC)-annexin V staining, the cytotoxicity of ART in HOS cells occurs through apoptosis. With ART treatment, cytosolic cytochrome *c* was increased, Bax expression was gradually upregulated, Bcl-2 expression was downregulated, and caspase-9 and caspase-3 were activated. Thus, the intrinsic apoptotic pathway may be involved in ART-induced apoptosis. Cell cycle analysis by flow cytometry indicated that ART may induce cell cycle arrest at G₂/M phase. In nude mice bearing HOS xenograft tumours, ART inhibited tumour growth and regulated the expressions of cleaved caspase-3 and survivin, in agreement with in vitro observations. ART has a selective antitumour activity against human osteosarcoma HOS cells, which may be related to its effects on induction of apoptosis via the intrinsic pathway. The results suggest that ART is a promising candidate for the treatment of osteosarcoma.