Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
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Letter to the Editor:

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

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Received Oct. 20, 2012; Revision accepted Oct. 22, 2012
Crosschecked Nov. 7, 2012

doi:10.1631/jzus.B1200288
Document code: A **CLC number:** R96

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 metallopeptidase 7 (MMP-7) is also down-regulated (Zhao *et al*., 2011). In addition, arsenuate enhances the radio-sensitization of lung carcinoma cells. It mediates this effect by down-regulating cyclin B1 expression, resulting in augmented G_2/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 (Thanaketpaisarn *et al*., 2011). It also decreases TRAIL induced nuclear factor-κB (NF-κB) 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 G_0/G_1 phase arrest. Artesunate also augments iron-dependent mitochondrial apoptosis. Similarly, artesunate enhances the radio-sensitivity 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 G_2/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.

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