O06 Artesunate reduces cell growth and induces ferroptosis in therapy-resistant renal cell carcinoma cells

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Introduction & Objectives: Despite advances in the development of targeted therapies for advanced renal cell carcinoma (RCC), treatment leads to drug resistance. Artesunate (ART) derived from artemisinin, a compound used in Traditional Chinese Medicine (TCM), might be a new therapeutic option since it has already revealed anti-tumor activity in a wide variety of tumor entities. This study was designed to evaluate, for the first time, the anti-tumor activity of ART on therapy-sensitive (parental) and -resistant RCC in vitro.

Materials & Methods: RCC cell lines KTCTL-26, A498, 786-O, and Caki-1 were chronically treated with sunitinib [1 µM] to induce sunitinib resistance. Parental cells served as controls. Dose-response analysis for ART [1-100 µM] was performed to determine the optimal concentration for further treatment. Aside from investigating tumor cell growth, the effect of ART [10-30 µM] on proliferation (BrdU) was also explored. The distribution of RCC cells in the cell cycle phases, the expression and activity of cell cycle regulatory proteins and proteins of the Akt/mTOR pathway as well as apoptotic and ferroptotic effects were evaluated.

Results: ART induced a significant inhibition of tumor cell growth and proliferation in both parental and sunitinib-resistant RCC cells in a time- and dose-dependent manner, compared to untreated cells. Apoptotic effects were in general not detectable. However, ferroptosis, iron-dependent cell death, became apparent following ART application. Reduced growth and proliferation after ART exposure was further associated with cell cycle arrest in the G0/G1 phase and distinct modulations in the expression of cell cycle regulating proteins. Also the expression of proteins of the Akt/mTOR signaling pathway revealed considerable changes after ART exposure.

Conclusions: ART significantly inhibited the growth of parental and therapy-resistant RCC cells by ferroptosis and cell cycle arrest in the G0/G1 phase. Thus, ART could hold promise as a treatment option for patients with advanced therapy-resistant RCC. Further investigation is necessary to verify these findings.