Arsenic trioxide

Arsenic trioxide (As2O3), known as pi-shuang and the most toxic compound in traditional Chinese medicine, has been used as an antitumor agent for thousands of years. Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural phenol that has significant anti-bacterial, anti-fungal and antiaging activities. A study of Yen et al. from Taichung, Taiwan, aimed to examine the combined anticancer effects of As2O3 and resveratrol against human neuroblastoma SK-N-SH cells, and elucidate the underlying intracellular signaling.

SK-N-SH cells were treated with an extremely low-dose (2-4 μM) of As2O3 alone or combined with 75 μg/ml resveratrol for further comparisons. Cell viability, apoptotic signaling as well as synergistic cytotoxic effects were estimated using the MTT assay, microscopy observation, flow cytometric analysis for loss of mitochondrial membrane potential (MMP) and reactive oxygen species (ROS), and typical quantitative western blotting analysis. Student's t-test, and one- and two-way analysis of variance (ANOVA) were used for examination of significant differences.

The combined treatment was more effective than single treatment of As2O3 or resveratrol alone in suppressing cell viability, which correlated with the elevation of ROS levels. The intracellular mechanisms of cytotoxicity of As2O3 plus resveratrol were revealed as ROS accumulation and relative decrease of MMP, leading to activation of caspase-3 and -9, but not of caspase-1, -7 and-8. Combination treatment reduced the expression of B-cell lymphoma 2 (BCL2), BH3 interacting domain death agonist (BID), and BCL-x/L.

Combined treatment at extremely low concentration of two agents from natural products, As2O3 and resveratrol, has high potential as a cocktail of anticancer drugs for neuroblastoma [1].

Standard treatment for GBM is radiation (RT) and temozolomide (TMZ). Arsenic trioxide (ATO) is synergistic with RT based on several mechanisms of action previously identified, however not tested herein. The MTD of ATO, RT and TMZ was determined in a Phase I trial. We now present the combined Phase I/II data. Patients with newly diagnosed malignant gliomas were eligible for treatment. Patients were treated with RT (60 GY), TMZ (75 mg/m2 daily × 42 days) and ATO 0.20 mg/kg daily in week 1 then twice a week ×5 weeks, after completing RT they were treated with TMZ 5/28 for up to 12 months. MRIs were performed every 8 weeks. A total of 42 patients were enrolled in both the Phase I and II trials for this study treatment. Of the 42 enrolled patients (24 M and 18 W) the median age was 54 (24-80) and median KPS 90 (60-100). 28 patients had a GBM and 14 had anaplastic glioma (AG). All patients completed RT/TMZ/ATO and went on to maintenance TMZ. Median number of post RT cycles of TMZ was 4 (0-12). Median PFS was 7 m for GBM and 75 m for AG and median OS was 17 m for GBM and NR for AG. Best response was CR in 2, SD in 28, PR in 5 and PD in 7. There were no unexpected adverse events. Grade 3 toxicities likely attributable to ATO included prolonged Qtc (n = 1), elevated liver enzymes (n = 2 for ALT/n = 1 for AST) and elevated bilirubin (n = 1). Adding ATO to RT and TMZ is feasible with no increased side effects. The addition of arsenic did not improve overall survival in the GBM patients as compared to historic data. MGMT status was analyzed in 20 of the 42 patients where tissue was available for retrieval and MGMT testing [2].

1)

Yen CM, Tsai CW, Chang WS, Yang YC, Hung YW, Lee HT, Shen CC, Sheu ML, Wang JY, Gong CL, Cheng WY, Bau DT. Novel Combination of Arsenic Trioxide (As(2)O(3) Plus Resveratrol in Inducing Programmed Cell Death of Human Neuroblastoma SK-N-SH Cells. Cancer Genomics Proteomics. 2018

Nov-Dec;15(6):453-460. doi: 10.21873/cgp.20104. PubMed PMID: 30343279.
2)

Kumthekar P, Grimm S, Chandler J, Mehta M, Marymont M, Levy R, Muro K, Helenowski I, McCarthy K, Fountas L, Raizer J. A phase II trial of arsenic trioxide and temozolomide in combination with radiation therapy for patients with malignant gliomas. J Neurooncol. 2017 May 16. doi: 10.1007/s11060-017-2469-x. [Epub ahead of print] PubMed PMID: 28510787.