

Abstract # 4545

Anticancer activity of elesclomol correlates with low LDH levels and active mitochondrial respiration.

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Background: Elesclomol is a first-in-class investigational drug that induces apoptosis in cancer cells through the elevation of reactive oxygen species (ROS). In a Phase 3 trial in metastatic melanoma, the level of baseline lactate dehydrogenase (LDH) in patients emerged as an important prognostic factor for treatment outcomes with elesclomol. Our previous studies revealed that elesclomol selectively chelates copper and generates ROS via reduction of Cu(II) to Cu(I). Because this copper redox reaction can be influenced by changes in cellular metabolic properties, we investigated whether elesclomol activity is influenced by the balance of mitochondrial respiration (normoxic conditions, normal LDH activity) and glycolysis (hypoxic conditions, high LDH activity) in the cancer cell. In the studies presented herein, we evaluated elesclomol activity under several situations in which cells express high levels of LDH and mitochondrial respiration is reduced.

Results: First, an increase in the level of Hypoxia Inducible Factor-1 α (HIF1 α) protein, a transcription factor that induces expression of glycolytic enzymes including LDH, was observed in M14 melanoma cells at low oxygen level or high cell density. Elesclomol showed decreased cytotoxicity under both of these conditions. Second, we evaluated lines within the same cancer phenotype but showing distinct levels of HIF1 α , and found that the high-HIF1 α -expressing Caki-2 renal cancer line was resistant to elesclomol, while lower-HIF1 α -expressing renal cancer cell lines were sensitive to elesclomol. Third, we assessed HIF1 α levels and elesclomol activity in cells treated with CoCl₂, a chemical mimetic of hypoxia. High levels of HIF1 α induction were present in M14 cells treated with CoCl₂, and elesclomol was significantly less active in these cells. The addition of oxamate, which selectively inhibits LDH-A and activates pyruvate entry into mitochondria, restored the activity of elesclomol in the CoCl₂-treated cells. These results support the hypothesis that elesclomol is more active under normoxic conditions (normal LDH) and less active under hypoxic conditions (high LDH), consistent with the clinical findings.