Naphtoquinones as Substitutes of Menadione in Apatone™ Therapy

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Apatone™, a combination of menadione (2-methyl-1,4-naphthoquinone, VK3) and ascorbic acid (VC) is a new strategy for cancer treatment. Part of its effect on tumor cells is related to the cellular pro-oxidative imbalance provoked by the generation of hydrogen peroxide (H2O2) through naphthoquinone redox cycling. In this study, we attempted to find new naphthoquinone derivatives that boost the efficiency of H2O2 production and, thereby, potentially increase its efficacy for cancer treatment. The measurement of oxygen consumption, production of H2O2 and HPLC were used to detect the redox cycle of naphthoquinone derivatives provoked by their reaction with ascorbic acid and glutathione (GSH). The compound 2-bromo-1,4-naphthoquinone (BrQ) was approximately ten- and nineteen-fold more efficient than VK3 in terms of the consumption of oxygen and the production of H2O2, respectively. The ratio \([\text{H}_2\text{O}_2]/\text{consumed}/[\text{naphthoquinone}]\) consumed was 68 ± 11 and 5.8 ± 0.2 (µM/µM) for BrQ and VK3, respectively, which revealed the higher efficacy of BrQ as a catalyst for the autoxidation of ascorbic acid. Both VK3 and BrQ reacted with GSH, but BrQ was the most effective substrate. Part of the GSH was incorporated into the naphthoquinone, producing a nucleophilic substitution product (Q-SG). The depletion of BrQ by GSH did not impede its redox capacity since Q-SG was also able to catalyze the production of ROS. VK3/VC has already been submitted to clinical trial for treatment of prostate cancer and demonstrated promising results. However, the substitution of VK3 with BrQ will open new lines of investigation regarding this approach for cancer treatment.

Word Keys: Cancer; Apatone™; Ascorbic Acid; Hydrogen Peroxide; 2-Bromo-1,4-naphthoquinone

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