Abstract

Background and purpose: Cytarabine (Ara-C) is an effective anticancer drug in the treatment of hematologic malignancies and one of its common toxicities is neurotoxicity. Depending on the administration route and dose of cytarabine, toxicities such as myelopathy, necrotic leukoencephalopathy, peripheral neuropathy seizures, cerebral dysfunction and acute cerebellar syndrome have reported in exposed patients. It has suggested that cytarabine induces toxicity via mitochondrial DNA synthesis inhibition, impairment in oxidative phosphorylation, ATP depletion, ROS formation and oxidative stress. Therefore, we hypothesized that mitochondrial protective agents and antioxidants can reduce cytarabine-induced neurotoxicity.

Materials and Method: Twenty-four male Wistar rats were assigned into four qual groups include control group, Ara-C plus vitamin D group, vitamin D and Ara-C group. Vitamin D (500 U/kg, i.p.) was administered to animal once daily for 10 consecutive days, from the first to the tenth day. Ara-C was given with a daily dose of 70 mg/kg bw, from the eleventh to the fifteenth day, in all groups receiving cytarabine. The activity of acetylcholinesterase (AChE) and butrylcholinesterase (BChE), the concentrations of antioxidants (reduced glutathione and oxidized glutathione), oxidative stress (malondialdehyde) biomarkers, mitochondrial toxicity parameters (succinate dehydrogenase activity, mitochondrial swelling, mitochondrial membrane potential collapse and reactive oxygen species formation) as well as histopathological alteration in brain tissues were measured.

Results: Our results demonstrated that Ara-C exposure significantly decline the histopathological parameters, brain enzymes activity (AChE and BChE), levels of antioxidant biomarkers (GSH), mitochondrial functions, but markedly elevate the levels of oxidative stress biomarkers (MDA), Oxidized glutathione (GSSG) and mitochondrial toxicity. Almost all of the previously mentioned parameters (especially mitochondrial toxicity) were retrieved by betanin, vitamin D and thymoquinone compared to Ara-C group. These findings conclusively indicate that betanin, vitamin D and thymoquinone administration provides adequate protection against Ara-C-induced neurotoxicity through modulations of oxidative, antioxidant activities and mitochondrial protective (mitoprotective) effects.

Discussion: Altogether, the results of the current study showed that Ara-C is a potent neurotoxic substance and it can cause serious damages to the mitochondria and the vitamin D can ameliorate these damages by its antioxidant activity.

Key Words: Antineoplastic Drugs; Mitochondria; neurotoxicity; Neuroprotective Effect