Characterization of the painful peripheral neuropathy induced by oxaliplatin-based chemotherapy in balb-c mice

Oxaliplatin (OHP) is a platinum-based drug used as first-line chemotherapy for the treatment of metastatic colorectal cancer. It acts by inducing DNA crosslinks that result in apoptotic cell death of dividing cells. A major clinical issue in the use of this drug is the severe painful peripheral neuropathy (PN) that affect several cancer patients under OHP-based chemotherapy. Acute OHP-induced PN is characterized by transient paresthesias and dysesthesias enhanced by exposure to cold, while persistent sensory dysfunction is the hallmark of chronic PN. Rat models of OHP-induced PN have been successful in describing its patho-physiological features, but they do not allow to combine the studies on the neurotoxicity and the neuropathic pain of OHP with those on its antineoplastic activity since most cancer models are developed in mice.

We have characterized the effects induced by a chronic iv 4-week treatment with OHP (2qw) on balb-c mice through the measure of sciatic and digital nerves conduction velocities (NCV), the pathological/morphometrical analysis of dorsal root ganglia (DRG) and the assessment of the mechanical/thermal thresholds. Moreover, in order to investigate relevant spinal cord structures involved in neuropathic pain, the electrophysiological determination of spinal dorsal horn neurons electrical activity was measured.

OHP treatment induced a significant impairment of the NCV and of nerve action potential amplitude. At the light and electron microscope analysis, DRG of OHP-treated mice showed frequent multinucleolated neurons with eccentric nucleoli. Moreover, the morphometrical analysis of DRG evidenced neuronal atrophy. As demonstrated by the Von Frey and the heat/cold plate tests, OHP induced the development of significant mechanical allodynia and cold hyperalgesia, starting from the first week of treatment. Finally, the electrophysiological assessments performed in the spinal cord revealed that, despite the incapacity of the drug to cross the blood-brain barrier, OHP treatment induced a remarkable increase of the activity of the wide dynamic range neurons in the spinal dorsal horn.

Our results demonstrate that the chronic treatment with OHP is able to induce a painful neuropathy in a balb-c mice model. Therefore, this model allows to combine the studies on the OHP-related antineoplastic activity, peripheral neurotoxicity and pain and can be used as a reference in the preclinical discovery of new neuroprotective as well as of analgesic compounds.