IJAE
Vol. 118, n. 2 (Supplement): 51, 2013
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Chemotherapy-induced peripheral neuropathy in immunodeficient mice: new useful ready-to-use animal models

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Cisplatin, paclitaxel, and bortezomib represent the most employed chemotherapy regimens for the treatment of genitourinary cancers, breast and lung cancers and multiple myeloma. Nevertheless, their clinical use is often associated to the development of peripheral neuropathies characterized mostly by sensory alterations and pain (Argyriou et al., 2012).

Several rat models of chemotherapy-induced peripheral neuropathy (CIPN) had been established in the past to describe the mechanisms of its development and pathogenesis. However, only few cancer cell lines induce the development of cancer in the rat, while immunodeficient mice best allowed human cancers xenografts to study at the same time, the antineoplastic and neurotoxic effects of chemotherapy.

Here we characterized neuropathic pain, neurophysiological and neuropathological alterations induced by chronic chemotherapy in immunodeficient nude mice. Mice were treated with effective doses of cisplatin (4 mg/Kg, i.p), paclitaxel (80 mg/Kg, i.v) and bortezomib (0.8 mg/Kg, i.v) for a 4-6 weeks period. At the end of the 6th week all chemotherapy regimens determined a significant impairment of neurophysiologic parameters, mechanical allodynia and thermal hypo-or hyperalgesia. Light microscopy analysis of dorsal root ganglia (DRG) showed that bortezomib induced morphological alterations in the sensory neurons and satellite cells as dark inclusions and clear vacuolation throughout the cytoplasm. Moreover, sporadic episodes of neuronal degeneration were evident. DRG of cisplatin-treated animals showed severe neuronal atrophy. Moreover bortezomib induced moderate to severe axonal degeneration of the myelinated fibers in the sciatic nerves. More severe changes were induced by paclitaxel where also areas of fibers loss were frequently observed and rare pathological abnormalities were present in unmyelinated fibers. Similar changes were evident in paclitaxel-treated mice (degeneration at different stage of severity in myelinated fibers, enlargement of Schwann cells, fibers loss and dark inclusions in the unmyelinated fibers). These schedules demonstrated to be effective in mimicking clinical features of painful neuropathies and allows to combine the study of peripheral neurotoxicity of chemotherapy drugs to their anti-tumour activity against cancers of human origin.

Supported by a research grant from Fondazione Banca del Monte di Lombardia to P.M.

References

[1] Argyriou et al. (2012) Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol 82: 51-77.

Key words

Chemotherapy, peripheral neuropathy, immunodeficient mice, light microscopy, peripheral nerves, dorsal root ganglia.