EPOTHILONE B-INDUCED TOXIC EFFECTS ON PERIPHERAL NERVOUS SYSTEM: *IN VITRO* AND *IN VIVO* EXPERIMENTAL MODELS.

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Epothilones are a novel class of microtubule-targeting anticancer agents that have a similar mechanism of action to the taxanes (i.e. polymerization of tubulin dimers into microtubules and stabilization of preformed microtubules) but show antiproliferative activity in taxane-resistant tumor cells. In order to study the epothilone B (EpoB)-induced neurotoxicity in clinical practice we have investigated the EpoB toxic effect *in vitro* and we have characterized *in vivo* his general and neurological side effects in the Wistar and Fischer rats.
The *in vitro* experiment performed in Dorsal Root Ganglia explants showed a dose-dependent effect of EpoB exposure on neurite elongation; concentrations equal to 50nM or higher induced a significant reduction in neurite elongation after 24h and this effect was even more severe after 48h. A dose-dependent neurotoxic effect was confirmed in both *in vivo* studies. In these models EpoB peripheral neurotoxicity was investigated with neurophysiological, behavioral (Hot plate test) and pathological (morphologic and morphometric analysis, Intraepidermal Nerve Fibers density) methods. Moreover, in order to evidence the EpoB effect at the molecular level we focused on tubulin and myelin proteins. All the results consistently demonstrated that EpoB was more toxic in Fischer than in Wistar rats at the general and neurological levels in the dose range 0,25-1,5 mg/kg.
Our results describing the dose-dependent neurological effects of EpoB and demonstrating that tubulin hyper-polimerization occurs at neurotoxic doses can be a solid basis for future studies.

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