EFFECT OF DIFFERENT CHRONIC TREATMENT MODALITIES ON THE PERIPHERAL NEUROTOXICITY OF SAGOPILONE IN RATS: A MULTIMODAL ANALYSIS

A. Chiorazzi[1], N. Oggioni[1], C. Meregalli[1], F. Avezza[1], V. Rodriguez-Menendez[1], R. Lewin[2], D. Stoeckigt[3], H. Hoechel[3], G. Cavaletti[1]

[1] Dept. Neuroscience and Biomedical Technologies, University of Milano-Bicocca, Monza, Italy
[2] Toxicology
[3] Bayer Schering Pharma, Drug Metabolism and Pharmacokinetics, Berlin, Germany

Sagopilone is the first fully synthetic epothilone entered in clinical investigation for the treatment of solid tumors. Since peripheral sensory neuropathy is its major side effect, this study was aimed to provide a preclinical model to evaluate factors that might modulate this side effect. We investigated the general toxicity and the peripheral neurotoxicity of sagopilone administered with different doses and schedules in Wistar rats and we performed a PK/PD study. The aims of the study were to establish the effect of different infusion times (i.v. bolus, i.v. 30-min infusion, and i.v. 3-hr infusion) over a 4-week treatment period; to evaluate the effect on nerve conduction velocity (NCV), to assess whether these schedules have an impact on peripheral neurotoxicity; to allow PK/PD modelling during the first 24 hours after infusion

After 2 weeks, a trend toward a different peripheral neurotoxicity (bolus > 30-min infusion > 3-hr infusion) could be assessed at the pathological and neurophysiological levels with both doses, but this trend was no longer present after 4 weeks. When sagopilone concentrations were measured in brain, sciatic nerve, liver and kidney a linear relationship with the PK parameters (AUC(0-24h), C_{max}) was observed. Sagopilone concentrations in sciatic nerve above 100 ng/g 24 hr after the 4^{th} administration were associated with a reduction in NCV. A clear dose-dependence of NCV reduction on the level of systemic exposure was not observed but there was a time- dependence with more severe effects after 4 weeks.

Both infusion duration of sagopilone had no consistent effect on PK parameters and on NCV; however, bolus was associated with higher AUC. Although lowest mean NCV values were observed at highest AUC values after 2 weeks, this relationship between AUC or C_{max} and NCV impairment was no longer evident at the end of the study. C_{max} and AUC values had a significant correlation across the study, therefore, the C_{max} – NCV relationship was very similar to the AUC – NCV data.

In conclusion, this study shows that the combination of neuropathological and neurophysiological investigations should be associated with PK/PD studies to obtain a better insight in the time course and severity of the peripheral neurotoxicity of sagopilone.