**Attenuation of vincristine-induced peripheral neuropathy through targeting OATP1B2 in mice**

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**BACKGROUND**

Vincristine (VCR) is a widely used chemotherapeutic drug for the treatment of many cancers, but its clinical use is associated with a dose-limiting peripheral neurotoxicity. Although the mechanistic basis of vincristine-induced peripheral neuropathy (VIPN) remains largely unknown, prior investigations have demonstrated that a great exposure of peripheral sensory nerves present in dorsal root ganglia (DRG) to VCR which leading to the initiation of neurotoxicity. We hypothesis that identification of a transporter-mediated mechanism of neuronal cellular uptake of VCR in DRG may shed light on the etiology of neurotoxicity and may lead to the development of novel therapeutic interventions aimed at targeting this initiating mechanism to limit exposure of the DRG to VCR.

**METHODS**

VCR uptake profile was performed on HEK293 cells transfected with hOATP1B1, hOATP1B3, or mOATP1B2. Gene expression OATP1B1 and OATP1B3 was measured on Human DRG total RNA using rt-PCR. VIPN was measured by the Von Frey Hair test, Thermal hyperalgesia test, and electrophysiology test on wild-type and OATP1B2 deficient mice before and after acute and/or chronic treatment of VCR. Systemic and tissue exposure of VCR in wild-type and OATP1B2 deficient mice were determined by UPLC-MS/MS. The uptake and cytotoxicity of VCR in the presence of nilotinib (0.2 or 1M) were measured in 5 leukemia cancer cell lines.

**RESULSTS**

We firstly confirmed that VCR could be transported in HEK293 cells overexpressing mouse OATP1B2 and human OATP1B3 homolog proteins (*P* < 0.05). To support the hypothesis that the ability of OATP1B1 and/or OATP1B3 to facilitate neuronal uptake of VCR is of clinical interests, we confirmed the presence of OATP1B3 and absent of OATP1B1 mRNA in pooled human DRG. VCR induced acute (*P* < 0.05, Von Frey test) and chronic (*P* < 0.05, Von Frey, heat plantar test, and sciatic nerve amplitude) forms of neurotoxicity in an OATP1B2-dependent manner, while genotype status did not alter systemic exposure of VCR. Pretreatment of 100mg/kg of oral nilotinib significantly prevented VCR-induced sensitivity to mechanical allodynia, thermal hyperalgesia, and sciatic nerve amplitude (*P* < 0.05) in wild-type mice. The uptake and cytotoxic effects of VCR in leukemia tumor cells were not negatively influenced by nilotinib.

**CONCLUSION**

In this study, we identified OATP1B-type transporters as a mediator for VIPN. The function of this transport system can be inhibited by tyrosine kinase inhibitor nilotinib, without compromising anticancer properties of VCR. These findings provide a rationale for the future development of the intervention strategy using transporter inhibitors to mitigate a debilitating side effect associated with VCR.

References:

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