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Commentary

Major Risk Factors for Acquiring Ifosfamide-Induced Encephalopathy

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DESCRIPTION

Ifosfamide with doxorubicin is a common therapy for both localized and metastatic Soft Tissue Sarcomas (STS). Ifosfamide is a nitrogen mustard family oxazaphosphorine-type chemotherapy medication. It functions as an alkylating agent for DNA. Ifosfamide is an isomeric counterpart of cyclophosphamide; both are prodrugs that must be activated by hepatic metabolism. The active molecule (ifosfamide mustard) is formed by metabolizing the prodrug to 4-hydroxy-ifosfamide, which is subsequently catalyzed by numerous CYP450 isoenzymes. Ifosfamide also has another metabolic route, hepatic N-dechloroethylation, which is particularly catalyzed by cytochromes CYP3A4 and CYP2B6.

This second route produces particular chemicals such as chloroacetaldehyde, 2-dechloroifosfamide (2d-ifosfamide), and 3-dechloroifosfamide (3d-ifosfamide). Ifosfamide may cause a number of adverse effects in patients. Some are common and occur with other chemotherapies (asthenia, hematological toxicity, nausea/vomiting, alopecia), whereas others are specific to the nitrogen mustard family and thus occur with cyclophosphamides (bladder toxicity by vesical elimination of caroling, a mucosal irritant metabolite requiring chelation by concomitant administration of mesa). However, individuals using ifosfamide may experience unique side effects, some of which are severe, such as renal (tubulopathy) and neurological (encephalopathy) damage. The build-up of ifosfamide's distinct metabolic products, 2d-ifosfamide (considered the key surrogate marker for toxicity), *INVITRO*-ifosfamide, and chloroacetaldehyde, is thought to be the source of these specific toxicity profiles. In retrospective studies, the frequency of neurotoxicity ranges from 4% to 60%.

Furthermore, due to the retrospective nature and limited number of existing series, the risk factors for developing ifosfamide-induced encephalopathy are poorly recognized. One of these elements has been considered as aprepitant co-administration. Aprepitant, an NK1 receptor antagonist, is mostly metabolized by CYP3A4 in the liver. It acts as a competitive enzyme inhibitor of CYP3A4, although it can also serve as an enzyme inducer, the impact of which varies over time (Duran). Furthermore, multiple case studies have clearly pointed to the function of aprepitant in the development of ifosfamide-induced encephalopathy.

The incidence of an acute encephalopathy in a patient on ifosfamide, with a concomitant rise in exposure to 2d-ifosfamide and 3d-ifosfamide by 67% and 37%, respectively, due to aprepitant co-medication.

A prospective research that included a pharmacokinetic evaluation of unmodified ifosfamide (no metabolite was investigated) and randomizing aprepitant co-administration in a limited sample of patients during ifosfamide medication found no pharmacokinetic interaction.

Finally, no preclinical (*in vitro* or animal) animal investigations to investigate this drug-drug interaction have been conducted. The present study's goal is to use a population pharmacokinetic strategy to examine plasma concentrations of ifosfamide and some of its metabolites. We want to examine if aprepitant is a covariate as a drug-drug interaction culprit of ifosfamide pharmacokinetics in STS patients who didn't get it in cycle 1 but needed it in cycle 2 due to poor digestive tolerance in the first cycle.

Ifosfamide is a relatively new chemotherapeutic medication that has been shown to be successful in the treatment of a variety of solid tumours in both children and adults. Nephrotoxicity, characterized by glomerular damage, is a serious issue that limits its usage; this sometimes includes signs of Fanconi syndrome, such as phosphaturia, magnesuria, and acidosis. Ifosfamide medication can result in significant and long-term renal function loss.

However, while ifosfamide is not especially hazardous to glomerular or tubular cells *in vitro*, a toxic metabolite is likely—a concept supported by the known involvement of acrolein in the toxicity of a comparable medication, cyclophosphamide.

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