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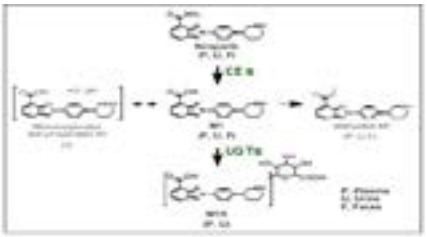
Pharmacokinetics of the poly (ADP-ribose) polymerase inhibitor (PARPi) niraparib

Statement of the Problem: Niraparib (ZEJULA™) is a highly selective inhibitor of PARP1&2, approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Here, we present the pharmacokinetic profile of niraparib.

Methodology & Theoretical Orientation: The pharmacokinetics and disposition of niraparib were comprehensively evaluated in preclinical *in vitro* and *in vivo* experiments and in three clinical studies aimed at characterizing its absorption, distribution, metabolism, and elimination.

Findings: Niraparib was highly bioavailable (F≈73%) with dose-proportional exposure (30–400 mg) and a consistent accumulation ratio (R≈2) following multiple daily doses in patients. The Vd/F of niraparib was 1220 L in cancer patients, indicating extensive tissue distribution. This was consistent with niraparib's distribution to rat brain, monkey cerebrospinal fluid, and xenographic tumors, and with its high permeability coefficient (Papp=12–18×106 cm/s) in cultured cells. The primary metabolic pathway via the liver (carboxylesterase-catalyzed amide hydrolysis) led to the formation of an inactive acid metabolite (M1), which is subjected to glucuronidation. Cytochrome P450 enzymes played a negligible role in niraparib metabolism in patients. Niraparib was comparably eliminated via the renal and fecal routes, and exhibited a long terminal half-life (≈2 days), supporting a daily dose regimen. The high recovery of niraparib and its metabolites (86%), accumulating within 21 days in the excreta of patients, suggests minimal long-term body retention.

Conclusion & Significance: Niraparib's ADME, characterized by high cell permeability and extensive tissue distribution, is consistent with its demonstrated anticancer activity.



Biography

Zhi-Yi Zhang is a Senior Director at TESARO Inc., an oncology-focused biopharmaceutical company in Waltham, MA, USA. He currently leads a group in Clinical Pharmacology and Drug Disposition supporting the development and regulatory submission of several drug candidates in the late phase of the Tesaro pipeline. Before joining TESARO, he worked at several other biopharmaceutical companies, leading efforts to characterize the absorption, distribution, metabolism, and elimination and drug-drug interactions of small molecule drug leads and candidates at Eisai Inc., and CombinatoRx Inc. He received his Medical degree at Fudan University Medical School, China; MS in Department of Environmental Sciences at Rutgers University, USA, and his PhD in Department of Environmental Health and Toxicology at State University of New York at Albany, USA. He completed his Post-doctoral training in Toxicology Division, Department of Chemistry, Massachusetts Institute of Technology, USA.

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