Gemcitabine Prodrug LY2334737

National Cancer Institute

Source

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An orally available valproic acid prodrug of gemcitabine, a broad-spectrum antimetabolite and deoxycytidine analogue with antineoplastic activity. Upon administration, gemcitabine prodrug LY2334737 is hydrolyzed by carboxylesterase 2 (CES2) and releases gemcitabine systemically over a period of time consistent with formation rate-limited kinetics. In turn, gemcitabine is converted into the active metabolites difluorodeoxycytidine diphosphate and triphosphate (dFdCDP and dFdCTP) by deoxycytidine kinase. dFdCDP inhibits ribonucleotide reductase, thereby decreasing the deoxynucleotide pool available for DNA replication; dFdCTP is incorporated into DNA, resulting in premature termination of DNA replication and eventually the induction of apoptosis. Compared to gemcitabine, this prodrug is able to avoid hydrolysis in enterocytes and the portal circulation thus avoiding first pass metabolism and increasing systemic gemcitabine availability. In addition, the slow release of gemcitabine may enhance efficacy while lowering toxicity. CES2, a serine ester hydrolase, is expressed in certain tumors which may allow for increased conversion of gemcitabine at the tumor site thus increases cytotoxicity.