

O. Shonukan
A.H. Dantzig
S. Kloeker-Rhoades
I. Garcia-Ribas

Eli Lilly Company,
Indianapolis, IN, USA

Development of LY2334737, an oral gemcitabine prodrug for continuous administration. Perspectives for the therapy of mature T-cell and NK-cell lymphomas



Gemcitabine (Gemzar) is a fluorinated pyrimidine nucleoside analogue that demonstrated a high schedule-dependency during its development for the therapy of diverse malignancies. This schedule-dependency may depend on the steps that are required to induce cytotoxic activity, and include intracellular uptake by specific nucleoside transporters and the effect on cancer cells at the G1 and S phases of the cell cycle. Gemzar is currently approved to be administered weekly at 1000-1250 mg/m², either as a single agent or in combination with other agents for the therapy of several solid tumors. Gemcitabine also has activity in Hodgkin's and in several types of non-Hodgkin's lymphoma including some subsets of peripheral T cell lymphoma.

LY2334737 is an oral gemcitabine prodrug in which gemcitabine is linked to valproic acid via an amide bond, enabling it to

bypass hydrolysis in enterocytes and portal circulation, thereby avoiding the extensive first pass metabolism that occurs with unmodified gemcitabine. Circulating levels of LY2334737 are detectable several hours after oral administration. In addition, a gradual release of gemcitabine following cleavage of the amide bond may ensure that more cancer cells are exposed to effective cytotoxic levels of gemcitabine as they enter G1/S phase of the cell cycle, to enhance efficacy. The lower peak plasma concentrations of gemcitabine that are achieved with LY2334737 may also result in lower toxicity when compared to bolus intravenous gemcitabine, thus resulting in a high therapeutic index. Phase I trials of this agent either as monotherapy or in combination with other agents are currently underway. Exploration of the role of this compound in the therapy of mature T-cell and NK-cell lymphomas is planned.