Nucleotide Analog Prodrug NUC-3373

National Cancer Institute

Source

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A phosphoramidate-based prodrug of the monophosphate (MP) form of 5-fluoro-2'-deoxyuridine (FUdR; FUDR), the active metabolite of fluorouracil (5-FU), an antimetabolite fluoropyrimidine analog of the pyrimidine nucleoside, with potential antineoplastic activity. Upon administration of the nucleotide analog prodrug NUC-3373, NUC-3373 is readily taken up by tumor cells. In the tumor cell, the phosphoramidate moiety is removed and NUC-3373 is converted to its active form FUDR-MP. In turn, FUDR-MP binds to and inhibits thymidylate synthase (TS), resulting in the depletion of thymidine triphosphate (TTP) and thus DNA synthesis. With the phosphoramidate moiety attached to FUDR-MP, NUC-3373, compared to 5-FU, is more lipophilic and accumulates in cancer cells by passive diffusion and does not require a nucleoside transporter, thereby generating higher intracellular concentrations. In addition, compared to 5-FU, once inside the cell FUDR-MP does not need to be phosphorylated and is already in its active form. Unlike 5-FU, NUC-3373 does not get deactivated or converted into toxic metabolites by dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP), which leads to both a longer half-life and less toxicity.