

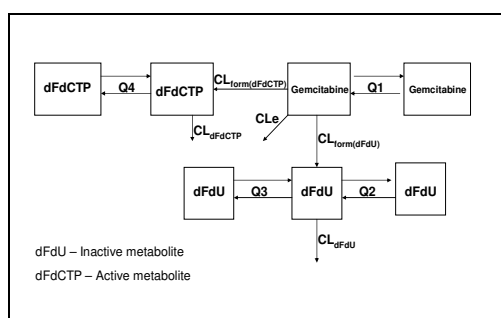
## Title: Pharmacokinetics of Gemcitabine and Its Metabolites in Patients with Solid Tumors

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**Objectives:** Gemcitabine (2',2'-difluorodeoxycytidine, dFdC) a nucleoside analogue, is approved as a first-line combination chemotherapeutic agent for treatment of pancreatic, non-small cell lung (NSCLC) and breast cancer, and second-line therapy in combination with carboplatin for treatment of ovarian cancer. After administration, gemcitabine undergoes metabolism by plasma and liver cytidine deaminase enzyme to form 2',2'-difluorodeoxyuridine (dFdU), a compound with little antitumor activity. Gemcitabine also undergoes intracellular metabolism by nucleoside kinases to form the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides, leading to inhibition of DNA synthesis. Exposure of dFdCTP has only been partially characterized – within the first 3 hours of drug administration the C<sub>max</sub> varies up to 12-fold in subjects receiving the same dose [1]. Accurate information on total exposure and formation clearance of dFdCTP is lacking. To better characterize the relationship between parent, inactive-, and active-metabolites, a comprehensive pharmacokinetic model is needed. The Aims of this study are 1) to characterize the pharmacokinetics of gemcitabine and its metabolites in patients with cancer, and 2) identify factors that are associated with gemcitabine pharmacokinetic variability.

**Methods:** Human subjects with solid tumors (e.g., NSCLC, breast, and pancreatic adenocarcinomas)  $\geq 18$  years of age, and receiving gemcitabine are being recruited to participate in this study. Demographics, concurrent medications, genomic DNA, and toxicity data are being collected. Plasma is being collected to measure gemcitabine and dFdU, and peripheral blood mononuclear cells (PBMC's) to measure intracellular dFdCTP. Pharmacokinetic sampling of plasma and PBMC's is at the following times: pre-dose, 5, 15, 30, 45 min, and 1.25, 1.5, 2, 6, 24, 48, and 72 hr after the end of infusion. Gemcitabine, dFdU, and dFdCTP are measured with validated UV-HPLC assays. Pharmacokinetics analysis is done by standard two stage approach. Figure 1 shows the compartmental pharmacokinetic model used for the analysis. Pharmacokinetic parameters were estimated by weighted least squares regression analysis using ADAPT-II program [2]. More than 95% of gemcitabine is cleared by its metabolism to dFdU [3]. For the analysis, the clearance of gemcitabine through excretion was fixed to 10 L/hr, which is about 5% of the reported literature value of total clearance of 185 L/hr [3]. The selection of the pharmacokinetic model was based on the CV of the parameters estimates, AIC and residual plots of standardized weighted residual versus times and predicted concentration.



**Figure 1. The compartmental pharmacokinetic model for gemcitabine, dFdU and dFdCTP.**

**Results:** A total of 10 Females and 12 Males have been enrolled in the study. The mean age is 61 years (range 20 to 87 years). Doses ranged from 600 to 1200 mg/m<sup>2</sup>. The pharmacokinetic model describing the concentration time profile of most of the patients consisted of 2 compartments for gemcitabine, 3 compartments for dFdU and 2 compartments for dFdCTP. The mean (SD) for pharmacokinetic parameters is summarized as follows: gemcitabine – CL<sub>total</sub> 487.2 (183.8) L/hr, V<sub>ss</sub> 175.9 (99.3) L, AUC 16.6 (7.90)  $\mu$ mol-hr/L, and t<sub>1/2 $\beta$</sub>  15 (7) min;

dFdU –  $CL_{\text{form(dFdU)}}$  474.2 (182.4) L/hr,  $V_{\text{ss}}$  196.7 (69.6) L,  $CL_{\text{dFdU}}$  6.90 (4.90) L/hr and AUC 47.8 (37.4) mmol-hr/L; dFdCTP –  $CL_{\text{form(dFdCTP)}}$  3.05 (2.70) L/hr,  $CL_{\text{dFdCTP}}$  0.19 (0.19) L/hr, AUC 242.1 (150.6) pmol-hr/ $10^6$  cells and  $t_{1/2-\beta}$  7.8 (2.8) hr. The relation between gemcitabine infusion rate and formation clearance of dFdCTP was negatively correlated ( $r = -0.76$ ).

**Conclusions:** In conclusion, this study is first to evaluate the formation clearance of the active metabolite of gemcitabine. Pharmacokinetic parameters of gemcitabine and its metabolites are consistent with those reported in literature. Future directions involve the population analysis of the data to identify patient specific covariates affecting the pharmacokinetics of gemcitabine and its metabolites.

#### **References:**

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