PATHWAY-BASED PHARMACOGENOMICS OF GEMCITABINE PHARMACOKINETICS IN PATIENTS WITH SOLID TUMORS

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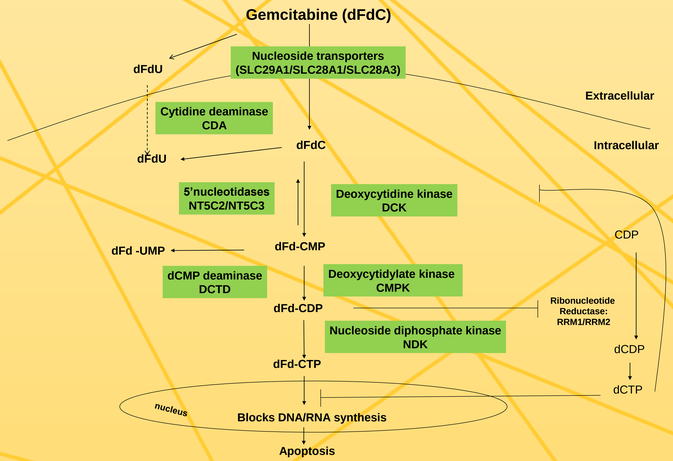
INTRODUCTION

- Gemcitabine (2',2'-difluorodeoxycytidine, dFdC) is an anticancer drug used against solid tumours
- It is a prodrug that is transported into cells by equilibrative and concentrative nucleoside transporters (ENTs and CNTs) followed by a series of phosphorylation steps for conversion to its active diphosphorylated and triphosphorylated forms, dFdCDP and dFdCTP
- Cytidine deaminase (CDA) rapidly metabolizes Gemcitabine to a less potent metabolite, 2',2'-difluorodeoxyuridine (dFdU) which is excreted into the urine
- Expression of genes in the gemcitabine pharmacokinetic (PK) pathway has been implicated in drug response and toxicity
- The current study involves a population pharmacokinetic analysis of gemcitabine in solid tumor patients to investigate genetic polymorphisms influencing the clearance of gemcitabine, dFdU and formation clearance of dFdCTP.



OBJECTIVE

To identify genetic polymorphisms responsible for variations in pharmacokinetics of gemcitabine in solid tumor patients.

METHODS

- Patients (n=40): adult (≥ 18 years old) patients diagnosed with solid tumors for which treatment with intravenous gemcitabine, either as single agent or in combination with other chemotherapeutic drugs, was already planned by clinicians.
- Blood samples were obtained at the following times: pre-infusion, 5, 15, 30, 45 min, and 1, 1.25, 1.5, 2, 6, 24, 48 and 72 hours after the end of gemcitabine infusion.
- Gemcitabine and dFdU concentrations in plasma and intracellular dFdCTP levels in PBMCs were measured with HPLC-UV and LC-MS/MS.
- Population pharmacokinetic analysis of gemcitabine and its metabolites, dFdU and dFdCTP, was performed with NONMEM VII.

- SNP Genotyping of the following genes was performed using MALDI-TOF based sequenom assay: DCK, SLC29A1, SLC28A1, SLC28A3, NT5C2, NT5C3, CDA, DCTD, CMPK and CTPS.
- Pharmacogenomic association was assessed using Wilcoxon rank-sum test and Kruskal-Wallis one-way analysis of variance by ranks (significance at $p < 0.05$).

Summary of SNPs genotyped in patients

Gene	Promoter/5'UTR SNPs	Coding SNPs	3' UTR SNPs
CDA	3	2	1
CMPK	0	3	3
CTPS	2	2	3
DCK	0	0	2
DCTD	0	1	3
NT5C2	2	2	1
NT5C3	0	3	0
SLC28A1	0	0	0
SLC28A3	1	0	1
SLC29A1	1	1	2

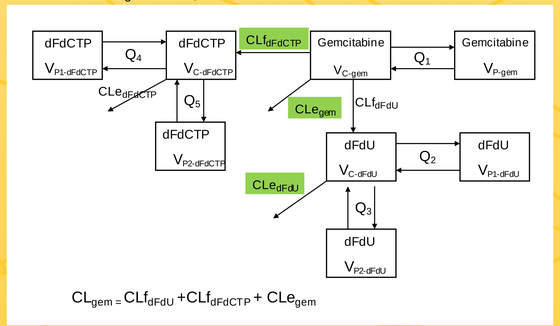
RESULTS

Patient Characteristics

Patient Characteristics	Median (Range)
Age (years)	64 (20-87)
Sex	22 females, 18 males
Weight (Kg)	79 (58-132)
Height (m)	1.7 (1.54 – 1.92)
BSA	1.92 (1.63-2.54)
SCR	0.90 (0.58-1.67)
Race	Caucasians – 40
Gemcitabine doses (mg/m^2)	1000 (600-1500)
Rate of Infusion (mg/m^2/min)	30.3 (8.11 – 49.52)

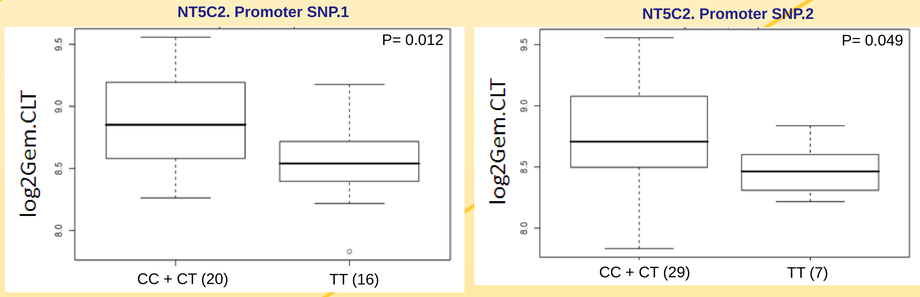
Pharmacokinetic model for gemcitabine, dFdU and dFdCTP

- A total of 335 gemcitabine, 454 dFdU and 373 dFdCTP concentrations were obtained.

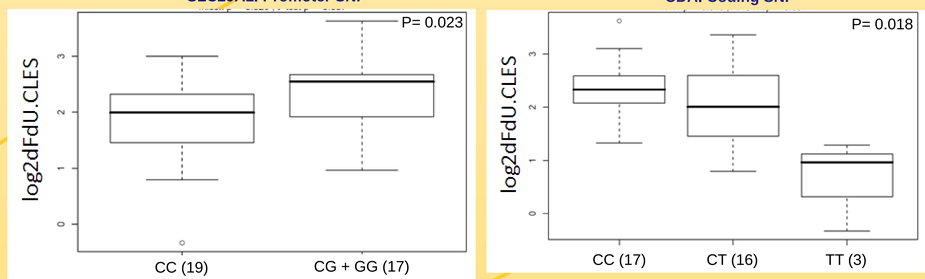


$$CL_{gem} = CLf_{dFdU} + CLf_{dFdCTP} + CLe_{gem}$$

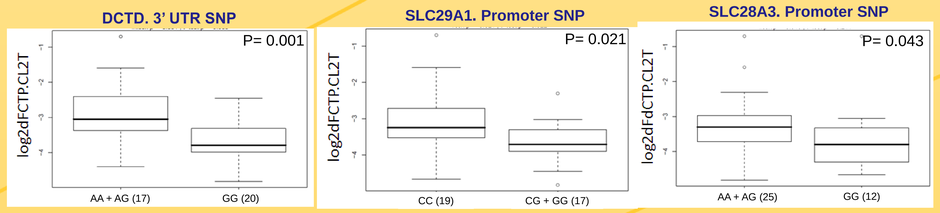
A. GEMCITABINE: Promoter SNPs in NT5C2 were associated with Gemcitabine clearance



B. dFdU: A coding SNP in CDA and a Promoter SNP in SLC29A1 were associated with dFdU clearance



C. dFdCTP: 3' UTR SNPs in DCTD and Promoter SNPs in SLC29A1 and SLC28A3 were associated with formation clearance of dFdCTP



CONCLUSIONS

- Gemcitabine metabolic pathway SNPs are associated with clearance of Gemcitabine, clearance of dFdU and formation clearance of dFdCTP.
- Such relationships may impact therapeutic outcomes for patients receiving gemcitabine.

ACKNOWLEDGEMENTS

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