Impact of CYP2C19 Polymorphism on the Pharmacokinetics of Nelfinavir in Pancreatic Cancer Patients
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Purpose
This study reports the pharmacokinetics of Nelfinavir and its active metabolite M8 in pancreatic cancer patients. We evaluated plasma levels of Nelfinavir and M8 and the influence of CYP2C19 polymorphism on the pharmacokinetics of Nelfinavir and M8 genotyped for CYP2C19 as extensive metabolizers (*1*1, n=33) and heterozygous poor metabolizers (*1*2, n=6).

Methods
Patients received Nelfinavir as normal dose (625 mg bid) and high dose (1250 mg bid). Steady-state plasma samples were analyzed by HPLC/UV assay. The genotypes of CYP2C19*1 and CYP2C19*2 were determined by the polymerase chain reaction-restriction fragment length polymorphism method.

Results
Pharmacokinetic profiles of Nelfinavir and M8 were characterized by wide interindividual variability, low apparent clearance (320-430 mLkg⁻¹h⁻¹) and prolonged half-life (6.8-8.1 h). The mean Cmax of Nelfinavir in CYP2C19*1/*1 patients was 3.89 ± 0.40 (n=3) and 5.12 ± 0.41 (n=30) µg/mL, while that of CYP2C19*1/*2 patients was 3.60 (n=1) and 6.14 ± 0.31 (n=5) µg/mL at the doses of 625 and 1250 mg Nelfinavir twice daily, respectively. For the M8 metabolite, the mean Cmax of CYP2C19*1/*1 patients was 1.06 ± 0.06 (n=3) and 1.58 ± 0.27 (n=30) µg/mL, while those of CYP2C19*1/*2 patients was 1.01 (n=1) and 1.23 ± 0.15 (n=5) µg/mL at the doses of 625 and 1250 mg Nelfinavir twice daily, respectively. The area under the plasma concentration-time curve (AUC₀⁻¹²h) values of Nelfinavir for CYP2C19*1/*1 patients was 28.90 ± 1.27 and 38.90 ± 4.99 µg/mLh, and for CYP2C19*1/*2 patients, AUC₀⁻¹²h was 28.20 (n=1) and 40.22 ± 3.17 (n=5) µg/mLh at the doses of 625 and 1250 mg Nelfinavir twice daily, respectively. The Cmax of Nelfinavir was significantly higher (p <0.05) in CYP2C19*1/*2 patients but there was no statistical difference in AUC₀⁻¹²h.

Conclusion
The CYP2C19*1/*2 genotype mildly affected the pharmacokinetic profiles of Nelfinavir and M8 in patients with locally advanced pancreatic cancer.

Figure. (a) Mean plasma concentration-time profiles of Nelfinavir. (b) Box plot showing AUC₀⁻¹²h of Nelfinavir in patients after oral administration of 1250 mg Nelfinavir twice daily.