Distinct pharmacokinetics and tissue distribution study of four structure similar epidermal growth factor receptor inhibitors using quantitation LC-MS/MS

Lu Wang[a], Miao He[a], Huixia Zhang[a], Manjunath Pai[b], Bo Wen[a], Hebao Yuan[a]*, Duxin Sun[a]*

[a] Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, USA

[b] Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, USA

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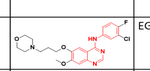
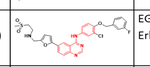
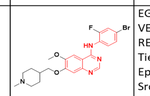
Purpose

Gefitinib, Erlotinib, Lapatinib and Vandetanib are all epidermal growth factor receptor (EGFR) inhibitors. They have similar target and similar quinazoline-based chemical structure, while they are used very differently in clinical, such as Gefitinib for lung cancer, Erlotinib for lung and pancreas cancer, Lapatinib for breast cancer and Vandetanib for thyroid cancer. This study aimed to investigate the distinct pharmacokinetics (PK) and tissue distribution of these four EGFR inhibitors, which may translated into the difference in their clinical usage and their adverse effects.

Tab 1. Structure, Efficacy, and toxicity summary of Gefitinib, Erlotinib, Lapatinib and Vandetanib

	Structure	Target	Dose	Clinical indication	PK parameters						
					Tmax (h)	F%	Cmax (ng/ml)	$AUC_{0\text{-}24}$ (ng·h/ml)	CL (L/h)	Vss (L)	$T_{1/2}$ (h)
Gefitinib (Iressa) 2003		EGFR	250 mg once daily	Non-small cell lung cancer (NSCLC)	5 (3-7)	57	193 (141-248)	4557	53.5	1400	22 (18-26)
Erlotinib (Tarceva) 2004		EGFR	150 mg once daily 100 mg once daily	NSCLC Pancreatic cancer	4	60	2002	42800	3.95	232	36.2
Lapatinib (Tykerb/Tyverb) 2007		EGFR, ErbB2	1250 mg once daily	Breast cancer	4	-	2430	36200	-	-	14.2
Vandetanib (Caprelsa) 2011		EGFRs, VEGFRs, RET, Brk, Tie2, EphRs, Src family kinases	300 mg once daily	Medullary thyroid cancer	6 (4-10)	-	129.5	22030	13.6	3818	456 (19 days)

Methods

Female CD-1 International Genetic Standardization (IGS) mice (6-8 weeks) were oral administered by cassette dosing of gefitinib, erlotinib, lapatinib and vandetanib (10 mg/kg per drug). At designated time points (0.08, 0.17, 0.25, 0.5, 0.75, 1, 2, 4, 7, 16, 24, 48, and 72 h), 3 mice were euthanized using isoflurane, and blood was immediately collected via cardiac puncture using a 25-G needle and 1-mL syringe (pretreated with sodium heparin). Plasma was collected after the blood was centrifuged at 14,500 rpm for 10 min. Tissues-brain, fat, heart, intestine, kidney, liver, lung, muscle, pancreas, spleen, stomach, bone, fat pad, uterus, and skin-were removed from the mouse and rinsed extensively in phosphate-buffered saline (pH 7.4). After tissue homogenization and protein precipitation, the concentration of each drug in plasma and different tissues was quantified by LC-MS/MS.

Results

LC-MS/MS quantification method

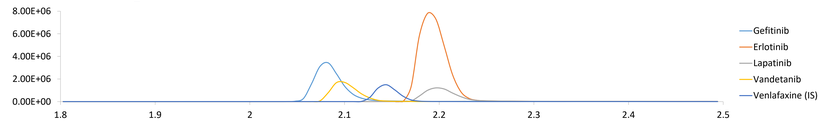


Fig 1. ESI-MRM chromatogram of a mixed-standard solution (100 ng/mL per drug)

Plasma and tissue drug concentration

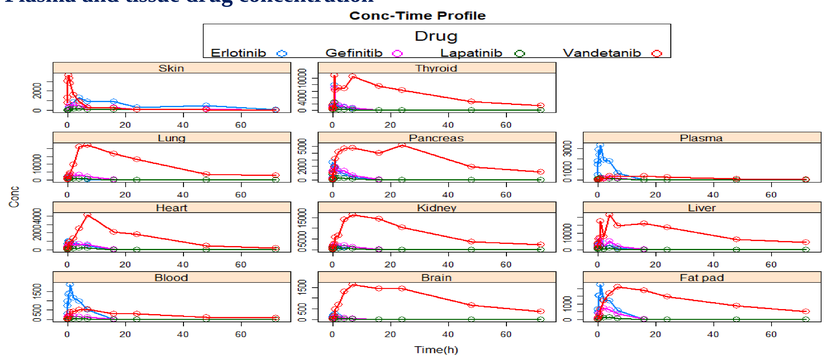


Fig 2. Different concentrations-time profiles in plasma and all tissues for four drugs

Tissue accumulation of drugs

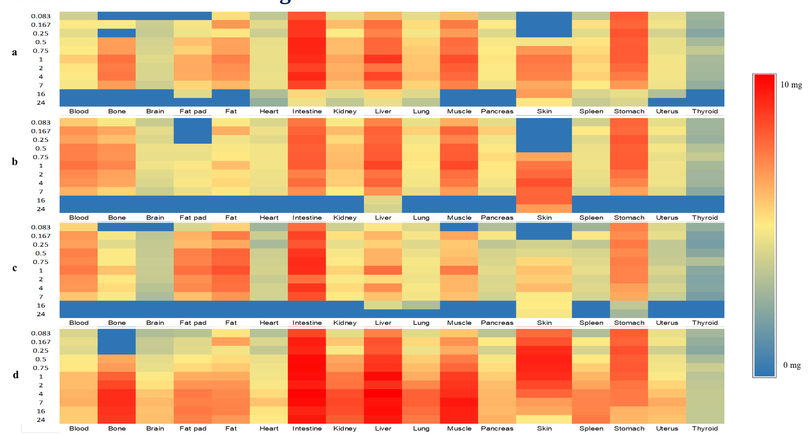


Fig 3. Total relative Gefitinib (a), Erlotinib (b), Lapatinib (c) and Vandetanib (d) amount in distinct tissues

Tissue distribution difference between Gefitinib, Erlotinib and Lapatinib

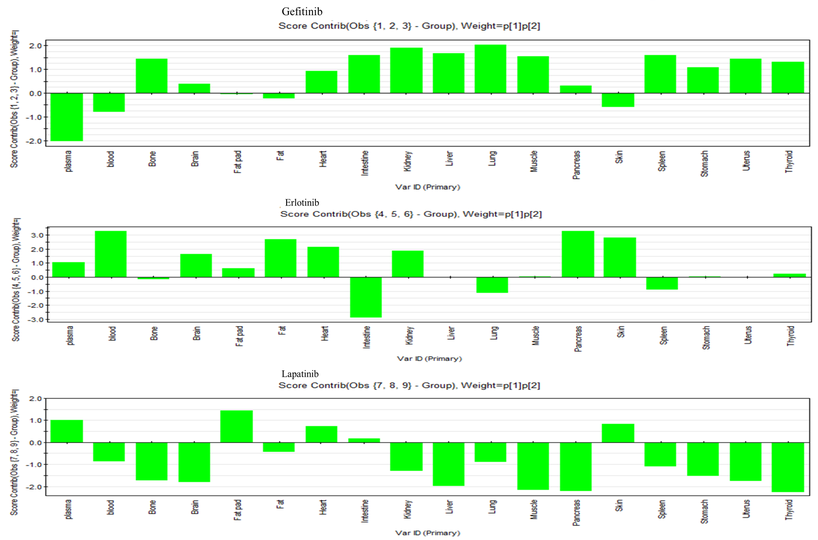


Fig 4. Tissue contribution plot of AUCs for Gefitinib, Erlotinib and Lapatinib after principal component analysis

Lung and pancreas are the most important tissue for Gefitinib and Erlotinib respectively, which consisted with their clinical use. Blood, brain, heart, kidney, skin has significant contribution for Erlotinib, and the related adverse effects could be found. Lapatinib has the poorest in-vivo behaviors, but fat pad still has positive contribution, which explains its clinical usage in breast cancer with a high dosage.

Conclusion

A systematic PK and tissue distribution study for four EGFR inhibitors has been presented using quantitation LC-MS/MS. Plasma and tissue concentration-time profile were compared. Same plasma profile can't output the same tissue distribution profile. And low plasma concentration could come out a good candidate with high tissue accumulation. Clinical indications and adverse effects of the drugs are related with their main accumulated tissues very well. It's demonstrated that tissue distribution behavior could be used to help understanding the clinical usage, efficacy and toxicity of a drug, which is important in the drug screening and preclinical study.

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UNIVERSITY OF MICHIGAN