Published in final edited form as:
J Thorac Oncol. 2010 August ; 5(8): 1311–1312. doi:10.1097/JTO.0b013e3181edf55c.

Serum concentrations of erlotinib at a dose of 25 mg daily

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Keywords

Epidermal growth factor receptor; EGFR; mutation; tyrosine kinase inhibitors; gefitinib; erlotinib; L858R; exon 19 deletions; lung cancer; non-small cell lung cancer

Letter to Editor:

Our group recently reported, in the journal, a retrospective review of the clinical efficacy of erlotinib at a dose of 25 mg daily for patients with metastatic non-small cell lung cancers (NSCLCs) with somatic mutations in the epidermal growth factor receptor (*EGFR*) gene (1). The 7 patients included in that study attained a response rate of 71.5% and a median progression-free survival of 17 months (95% CI, 6 – 35 months). We speculated that the serum concentrations achieved with erlotinib 25 mg/day were similar to the serum concentrations observed with gefitinib 250 mg/day. Based on published phase I trials for these EGFR tyrosine kinase inhibitors (TKIs), the mean serum trough concentration attained with gefitinib 250 mg/day was between 0.16–0.24 μg/mL or 0.35–0.53 μM (2); while the mean serum concentration measured with erlotinib 25 mg daily was approximately 0.22 μg/mL or 0.51 μM (3). However, at the time of our initial publication we had not measured the concentrations of erlotinib in any of our studied patients.

We now report erlotinib's serum concentration for 2 out of the 7 patients (1) initially described in our case series of a dose of erlotinib 25 mg/day and for an additional patient (4) treated with erlotinib 150 mg/day (Table). All patients had stage IV NSCLCs and received erlotinib orally. Erlotinib (molecular weight of 429.90) was measured using high performance liquid chromatography (HPLC) with ultra-violet detection (5). The measured serum concentration of erlotinib, by HPLC, in both patients receiving 25 mg/day exceeded 0.4 μM (Table); while the concentration measured for the patient receiving 150 mg/day exceeded 4 μM. Skin and gastrointestinal toxicities correlated with the serum concentration of erlotinib.

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Conflict of interest: No conflict of interest is stated.

These updated results further strengthen our clinical results, and provide additional evidence that a dose of erlotinib 25 mg/day can lead to serum concentrations that are similar to those previously reported with gefitinib 250 mg/day. At doses as low as 0.1 μM of either gefitinib or erlotinib, NSCLC cell lines with sensitizing *EGFR* mutation are inhibited and undergo apoptosis (6). Therefore, it is tempting to speculate that effective doses of gefitinib/erlotinib in NSCLC patients with sensitizing *EGFR* mutations are far below their maximum tolerated doses in humans. Prospective clinical trials of erlotinib at lower than approved doses are warranted, and will help define less toxic treatment strategies for NSCLC patients whose tumors harbor *EGFR* mutations.

Acknowledgments

Funding/Grant Support: This work was funded in part by grants from the National Institutes of Health (NIH) R00CA126026-03 (SK) and 2PA50-CA090578-07 (DBC, DGT, BYY); the American Association for Cancer Research 07-40-12-COST (DBC); a Career Development Award by the American Society of Clinical Oncology Cancer Foundation CDA-15431 (DBC); a Grants-in-Aid for Scientific Research by Japan Society for the Promotion of Science, 21590167 (HA); and a Research Fellowship Award by the National Medical Research Council, Ministry of Health, Singapore (WY).

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Table

Serum concentration of erlotinib in patients with stage IV *EGFR* mutated NSCLC

	Clinical and Molecular Characteristics				Erlotinib Concentration			Efficacy		Toxicity (grade - CTCAE)	
Patient (ref.)	**age (years)**	**sex**	**ethnicity**	***EGFR* mutation**	**daily dose erlotinib**	**erlotinib serum (μg/mL)**	**erlotinib serum (μM)**	**response (RECIST)**	**PFS (months)**	**rash/ pruritus**	**diarrhea**
1 (1)	64	F	Asian	delE746_A750	25 mg	0.19	0.44	PR	9	none (0)	none (0)
2 (1)	46	M	Asian	L858R	25 mg	0.38	0.88	SD	4	yes (1)	none (0)
3 (4)	74	F	Caucasian	L858R-L747S	150 mg	1.80	4.18	PR	6	yes (3)	yes (2)

EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; CTCAE, common terminology criteria for adverse events v3.0; M, male; F, female; RECIST, response evaluation criteria in solid tumors v1.0; PR, partial response; SD, stable disease; ref, reference.

J Thorac Oncol. Author manuscript; available in PMC 2011 August 1.