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William C. Klingensmith III*
Joseph R. Osborne
**Weill Cornell Medicine*
520 East 70th St., New York, NY 10021
E-mail: nid2697@nyp.org

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ABCG2- and ABCB1 Inhibition Using Supratherapeutic Doses of Erlotinib: Clinical Implications in the Treatment of Central Nervous System Metastases

TO THE EDITOR: We read with great interest the article by Bauer et al. titled "A Proof-of-Concept Study to Inhibit ABCG2- and ABCB1-Mediated Efflux Transport at the Human Blood–Brain Barrier." They concluded that ABCB1 inhibition by tariquidar (an ABCB1 inhibitor) was not able to enhance ^{11}C-erlotinib brain uptake, but supratherapeutic doses of erlotinib (a dual ABCB1/ABCG2 substrate) before PET scanning could increase ^{11}C-erlotinib brain uptake significantly, when 650 mg or more of erlotinib were administered (*1*). Previous research from our group using elacridar (also an ABCB1 inhibitor) and ^{11}C-erlotinib PET showed that elacridar was ineffective in blocking ABCG2 (*2*). The present study underlines the major barrier role of ABCG2, as it showed that ABCG2 was also insufficiently targeted by tariquidar to achieve significant inhibition of this efflux pump.

Tyrosine kinase inhibitors (TKIs) directed against epidermal growth factor receptor (EGFR), including erlotinib and osimertinib, are all substrates for ABCB1 and ABCG2 transporters. For erlotinib, we showed that ^{11}C-erlotinib uptake decreased on treatment with erlotinib (150 mg daily) in tumors, but also in liver tissue, due to EGFR saturation and lowering of the specific binding of ^{11}C-erlotinib to the EGFR target (*3,4*). However, Bauer et al. showed that supratherapeutic doses of erlotinib led to an increase in the brain uptake, probably through saturation of the ABCB1/ABCG2 efflux pumps leading to elevated nonspecific uptake of ^{11}C-erlotinib in the brain as no relevant target EGFR expression is expected in brain tissue.

There is a therapeutic interest in understanding how these efflux pumps can be influenced. Inhibiting erlotinib efflux could benefit EGFR mutation–positive non–small cell lung cancer (NSCLC) patients with metastases of the central nervous system, which are among the most difficult to treat. Especially, leptomeningeal metastases are often refractory to standard dose therapy as a result of lowered anticancer drug concentration in the cerebrospinal fluid. One strategy to achieve control is to use supratherapeutic doses of erlotinib, where doses of 1,500 mg (10 times the standard daily dose of 150 mg/d) once per week were shown to be effective (*5*). Although this regimen is successful in certain cases, it is restricted by higher toxicity. The Bauer et al. study showed a 27% increase of VT (volume of distribution) and a 94% increase of AUC (area under the curve) at 1,000 mg, implying a significant clinical benefit. However, they also encountered an increase of adverse events in this group up to the point where inclusion was discontinued. Results using a lower dose, that is, 650 mg, showed a similar increase in VT (23%) and still a significant increase in AUC (78%). This implies that this dose could be sufficient to overcome active efflux of erlotinib with less toxicity. This insight could open the door to different scheduling and dosing regimens.

The treatment landscape for EGFR mutation–positive NSCLC is also evolving. The FLAURA trial showed that osimertinib, a third-generation EGFR-TKI, was more effective than first-generation EGFR-TKIs such as erlotinib for both progression free-survival and overall survival, was better tolerable, and achieved excellent control of brain metastases (*6*). However, despite good brain penetration, leptomeningeal metastatic disease is still a challenge to osimertinib. Here, the present trial design could serve as an example to study the cerebral pharmacokinetics of next-generation EGFR-TKIs such as osimertinib.

Overall, the results of this well-designed and well-conducted study will help to optimize the treatment regimens in EGFR mutation–positive NSCLC patients with central nervous system metastases.

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Eveline A. van de Stadt*
Maqsood Yaqub
Idris Bahce
N.H. Hendrikse
**Amsterdam UMC, VUmc*
De Boelelaan 1117
Amsterdam, Netherlands 1081HV
E-mail: e.vandestadt@amsterdamumc.nl

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