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CLINICAL–PATIENT STUDIES

Gefitinib concentrations in human glioblastoma tissue

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Delivery of anticancer agents to solid tumors is not well investigated and studies analyzing drug concentrations in human tumor tissue, especially in the brain, are scarce.

In our institution, we have the opportunity to directly measure anticancer drug concentrations in glioblastoma (GBM) tumor tissue in correlation to plasma concentration. GBM patients with a relapse, however in good performance status are offered secondary surgery where appropriate and participation in a prospective trial with gefitinib [1]. Gefitinib is currently under scrutiny for the treatment of high grade glioma [2].

At least 5 days before re-operation, patients receive gefitinib 500 mg daily continuously until tumor progression or intolerable side effects. Patients on cytochrome P450 isoenzyme CYP3A4-inducing antiepileptic drugs (EIAE) have to change to a non-enzyme-inducing drug, due to predicted ensuing interactions of EIAE with gefitinib metabolism, reducing its systemic availability. The trial is approved by the local ethic committee and is registered within the National Library of Medicine Clinical Trials Database (www.clinicaltrials.gov, NCT00250887).

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Table 1 Gefitinib tumor and plasma concentrations

Pat. No.	GBM tissue (ng/g)	Plasma (ng/ml)
1*	24103	na
1*	8681	na
1*	11103	na
2	3132	247
3	4963	176
4	6218	181
5	2852	4
6	4730	127
7	3468	176

na: not assessed

*All three samples of this patient were collected on the same occasion

Here we report on surprisingly high tumor tissue levels of gefitinib from the first seven patients (Table 1). Tumor tissue and blood samples were snap frozen immediately upon removal and stored at –70°C for analysis (Laboratory Analytico Medinet B.V., Breda, NL). High performance liquid chromatography coupled to tandem mass spectroscopy was performed to determine drug concentrations, as described previously [3].

To our knowledge this is the first consecutive series of gefitinib concentrations in human brain tumor tissue. We suggest, that higher drug exposure is not required to treat glioma patients.

Further translational research will be performed with the tumor material to correlate responding patients to their tumor EGFR pathway activity and to define molecular markers predictive for response.

References

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