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A Neuropharmacokinetic Assessment of Bafetinib, a Second Generation Dual BCR-Abl/Lyn Tyrosine Kinase Inhibitor, in Patients with Recurrent High-Grade Gliomas

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Abstract

Purpose—The primary objective of this study was to use intracerebral microdialysis (ICMD) to determine the neuropharmacokinetics of bafetinib, a dual BCR-Abl/Lyn tyrosine kinase inhibitor that may have activity against gliomas.

Methods—A microdialysis catheter was placed into either peritumoral or enhancing brain tissue of 7 patients at time of tumor resection or biopsy. Twenty-four hours later, bafetinib was administered, 240 or 360 mg po, repeating the same dose 12 hours later. Dialysate samples were continuously collected for 24 hours, with plasma samples obtained in parallel. One to two weeks after finishing ICMD, patients were allowed to resume taking bafetinib continuously while being observed for toxicity and tumor response.

Results—Twenty-six dialysate samples per patient were collected (n=6) and analyzed for bafetinib by tandem mass spectrometry. Bafetinib concentrations in brain were below the lower limit of detection of the assay (0.1 ng/ml) in all samples except 1 from a single subject that was 0.52 ng/ml. The mean plasma bafetinib maximum concentrations after dose 1 and 2 were 143±99 and 247±73 ng/ml, respectively. Only 1 patient remained on treatment past 2 cycles, and no radiographic responses were seen.

Conclusions—Bafetinib does not sufficiently cross intact or disrupted blood-brain barrier, and therefore, systemic administration of bafetinib is not recommended when investigating this drug as a treatment for brain tumors. ICMD can be a valuable research tool in early drug development. Lead-in ICMD studies can be performed relatively quickly, requiring only a small number of patients, and without significantly disrupting standard cancer care.

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Keywords

intracerebral microdialysis; bafetinib; neuropharmacokinetics; brain tumor

1. Introduction

Bafetinib is a potent second generation breakpoint cluster region—Abelson (BCR-ABL)/Lyn tyrosine kinase inhibitor (TKI)^{1,2} which is currently being investigated as a treatment for Philadelphia chromosome-positive leukemia. In addition to inhibiting autophosphorylation of ABL point mutations, this dual TKI selectively inactivates Lyn³ and Fyn, which are members of the sarcoma family kinases. Analysis of glioblastoma samples detected increased Lyn kinase activity,⁴ which may contribute to its malignant phenotype. Co-activation of Fyn kinase with epidermal growth factor receptors promotes tumor invasion and survival in glioblastoma.⁵ *In vitro* studies of bafetinib alone or in combination with either temozolomide or erlotinib demonstrated activity against glioma cell lines.⁶ As a potent inhibitor of Lyn and Fyn, bafetinib may be effective in blocking the growth and spread of glioblastoma.

For other BCR-ABL TKIs, such as imatinib⁷⁻¹² and dasatinib,^{13,14} conflicting data exist as to how well they cross the blood-brain barrier (BBB). With bafetinib, preclinical rodent studies showed that after oral administration, concentrations in rat brain were approximately 10% of plasma levels.^{15,16} In mice, peak bafetinib concentrations in the brain occurred 2 hours after oral administration, achieving concentrations above the IC₅₀ for leukemic cell lines.¹⁶ However, bafetinib, like imatinib,^{17,18} is a substrate for P-glycoprotein (P-gp),¹⁶ a transmembrane drug efflux pump found in BBB. To investigate the potential of bafetinib as a treatment for brain tumors, we performed an intracerebral microdialysis study to assess its neuropharmacokinetics in patients with recurrent high-grade gliomas.

2. Patients and Methods

2.1 Determination of the fractional recovery of bafetinib by the microdialysis catheter

A 70 Brain Microdialysis Catheter (membrane length 10 mm; shaft length 100 mm; semipermeable membrane molecular weight cut off of 20,000 Da; ref. no. P000050, M Dialysis, Solna, Sweden) was submerged in a 15 mL conical centrifuge tube containing bafetinib (200 ng/mL) in artificial cerebrospinal fluid (CSF) [Perfusion Fluid CNS, ref. no. P000151, M Dialysis, Solna, Sweden], at 37° C. Artificial CSF perfused the catheter at rates of 0.5 or 1.0 µL/min. Dialysate samples (30 µL) were collected at regular intervals and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS).

2.2 Patient selection

To be eligible for participation in this pilot study, patients had to be ≥ 18 years old, have radiographic findings consistent with recurrent high-grade glioma, and be in need of tumor resection or biopsy. Other inclusion criteria were: a) Karnofsky performance status (KPS) ≥ 60%, b) recovery from toxicity of prior therapy, c) adequate bone marrow function (absolute neutrophil count ≥ 1500 cells/mm³ and platelet count ≥ 100,000 cells/mm³), hepatic

function (total bilirubin ≤ 2.0 mg/dL, serum levels of aspartate aminotransferase and alanine aminotransferase $\leq 3 \times$ the institutional upper limit of normal), and renal function (serum creatinine $\leq 1.5 \times$ the institutional upper limit of normal), d), a minimum of 4 weeks from previous chemotherapy (6 weeks from a nitrosourea), and e) QTc interval <480 msec on electrocardiogram.

Patients were excluded from study participation if they a) were taking hepatic enzyme-inducing anticonvulsants within 2 weeks prior to enrollment, b) were receiving chemotherapy, radiation, or enrolled in another clinical trial, c) had a coagulopathy or were taking anticoagulant therapy or medications that inhibit platelet function, d) were pregnant or breast-feeding, or e) had a serious medical or psychiatric illness that could potentially interfere with the completion of study treatment.

Participants gave written informed consent. The study was approved by the City of Hope Institutional Review Board (IRB), conducted under an Investigational New Drug Application (IND# 110189), and registered at ClinicalTrials.gov (NCT01234740).

2.3 Treatment plan

During surgery, if frozen section indicated the presence of recurrent tumor, the neurosurgeon inserted a microdialysis catheter (70 Brain Microdialysis Catheter, M Dialysis, Solna, Sweden) into residual tumor or peritumoral tissue within 5-15 mm of the resection cavity. After a post-operative non-contrast computerized tomography (CT) scan of the brain confirmed the location of the catheter, a pump (107 Microdialysis Pump, ref. no. P000127, M Dialysis, Solna Sweden), perfused the catheter with artificial CSF at a rate of $0.5 \mu\text{L}/\text{min}$. Contrast-enhanced brain magnetic resonance images (MRI) were obtained within 24 hours of surgery to serve as a baseline for assessing response and evaluate microdialysis catheter position (in enhancing versus peritumoral tissue) by creating a fused MRI/CT image.

At least 24 hours after surgery, study patients received an oral dose of bafetinib on an empty stomach: either 240 mg (patients 1-5), which was the maximum tolerated dose determined in a previous phase I study,¹⁹ or 360 mg (patient 6), with the same dose repeated 12 hours later. Dialysate samples were obtained hourly for 24 hours starting after the first dose. To stabilize bafetinib, $6 \mu\text{L}$ of 6% acetic acid was added to each microvial. Dialysate samples were immediately placed on dry ice and stored at -70°C until analysis. Plasma samples were obtained prior to each dose of bafetinib, and then 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after each dose of bafetinib.

After completing the microdialysis portion of the study, patients were allowed to resume taking bafetinib after recovery from surgery. Brain MRIs were performed after every 2 cycles to assess response. All observed toxicities were graded using Common Terminology Criteria for Adverse Events version 4.0. MacDonald Criteria²⁰ were used to assess radiographic responses.

2.4 Pharmacokinetic data analysis

Dialysate and plasma samples were analyzed for bafetinib using validated LC-MS/MS assays. Please see Supplementary Data for methodologic details.

2.5 Statistical analysis plan

The primary objective of this study was to evaluate the neuropharmacokinetics of bafetinib in patients with recurrent high-grade gliomas using intracerebral microdialysis and compare these data to plasma levels. Secondary objectives included describing toxicities and clinical benefit in this small cohort of patients with primary brain tumors. Based on our previous experience with using microdialysis to measure chemotherapy levels in the brain,²¹ we estimated that a sample size of 6-8 patients would be sufficient to characterize the neuropharmacokinetics of bafetinib.

3. Results

3.1 In vitro recovery results

In vitro recovery experiments determined that the fractional recovery of bafetinib at a flow rate of 0.5 $\mu\text{L}/\text{min}$ was 85-90%, compared to 60-70% at a flow rate of 1 $\mu\text{L}/\text{min}$.

3.2 Patient characteristics

Seven subjects were enrolled from December 2010 to June 2011. Microdialysis data were successfully collected from 6 patients. The catheter would not flush after placement in 1, and that patient decided not to continue on study. Table 1 shows the demographics of the 6 patients from whom microdialysis data were obtained. All had recurrent high-grade gliomas and were previously treated with brain radiation and chemotherapy. During microdialysis, patients took non-hepatic enzyme inducing anticonvulsants (mainly levetiracetam). All patients received post-operative dexamethasone. The median total daily dose of dexamethasone was 12 mg (range 4-40 mg).

3.3 Brain interstitial levels of bafetinib

Although a highly sensitive and validated analytical method was used to measure bafetinib in dialysate (lower limit of quantitation [LLOQ] = 0.5 ng/ml and detection [LOD] = 0.1 ng/ml), analysis of the 156 dialysate samples (26 per patient) showed no detectable bafetinib in brain extracellular fluid (ECF) with the exception of a single sample from patient 2, which was obtained 5 hours after the first dose of study drug. The concentration of bafetinib was 0.52 ng/ml. Although this patient had the second highest maximum plasma concentration (C_{max}) following dose 1 and a time to maximum plasma concentration (T_{max}) of 2 hours, there was no clear relationship between plasma and ECF levels.

The microdialysis catheters in the first 4 study subjects were placed in non-enhancing peritumoral tissue. Figure 1A shows an example of a fused image of a study patient's immediate post-operative non-contrast CT scan (in which the catheter tip is visible) and a contrast-enhanced MRI performed approximately 24 hours after surgery. This merged image documents that the microdialysis catheter was placed in non-enhancing tissue where BBB is relatively intact.

Because bafetinib was undetectable in nearly all dialysate samples from the first 4 patients, and since many drugs that cannot cross intact BBB may still pass through disrupted blood-tumor barrier, subsequent enrollment was restricted to patients undergoing biopsy only to assess bafetinib concentrations in enhancing tissue. Patients 5 and 6 had catheters placed within enhancing brain tissue (figure 1B). Furthermore, with IRB approval, patient 6 received a dose of 360 mg bid. Analysis of dialysate samples from both these patients, however, showed no detectable levels of bafetinib in brain ECF.

3.4 Plasma levels of bafetinib

Table 2 and figure 2 summarize the bafetinib plasma pharmacokinetic data. A total of 102 plasma samples (17 per patient) were collected. The mean C_{max} after dose 1 and 2 were 143±99 and 247±73 ng/ml respectively. The mean area-under-the-concentration-time curve to the last measured time point (AUC 0-12h) following dose 1 and 2 were 660±431 and 1174±534 ng/mlxhr, respectively. The average T_{max} following dose 1 and 2 were 6±4 and 5±2 hr, respectively. As depicted in figure 2, there was significant inter-patient variability in the plasma concentrations. The bafetinib plasma pharmacokinetic results from this study are similar to previously published data.¹⁹

3.5 Safety and efficacy

All participants tolerated the intracerebral microdialysis well. Two developed grade 3 toxicities at least possibly related to bafetinib. One participant experienced a grade 3 elevation of alanine aminotransferase, and the other developed bacterial meningitis approximately 3 weeks after tumor resection and placement of the microdialysis catheter. Although the meningitis was likely a late post-operative complication, an association with bafetinib could not be excluded.

There were no radiographic responses to bafetinib. Three patients developed progressive disease within 2 months of starting study drug. One patient from whom dialysate samples were collected, experienced neurologic decline after surgery and did not resume bafetinib. Only 1 patient remained on study treatment past 2 months. He received 6 cycles of bafetinib, with serial brain MRIs showing stable disease. However, once the microdialysis data were available, the slides from this patient's biopsy were re-reviewed by the study neuropathologist who concluded that the pre-biopsy radiographic findings most likely represented treatment effect from radiation (pseudoprogression). Therefore, the stable disease during bafetinib treatment was likely due to lack of tumor progression at the time of study enrollment rather than inhibition of tumor growth by bafetinib. The last patient to enroll was taken off study 2 weeks into his first cycle of bafetinib when the study was closed based on the final analysis of dialysate samples showing no detectable levels of bafetinib in the brain.

4. Discussion

Intracerebral microdialysis is a technique for continuously analyzing the concentration of a drug or biomolecule in the ECF of the brain without significantly disrupting tissue function.^{22,23} In this study, microdialysis was used to assess the neuropharmacokinetics of

bafetinib prior to initiating an efficacy study in glioma patients. Our findings suggest that bafetinib does not sufficiently cross an intact or disrupted BBB, and therefore, systemically administered bafetinib is not recommended for testing in phase II brain tumor clinical trials. Inhibition of Lyn and Fyn kinases is a reasonable glioma treatment strategy, and exploring an alternative route of delivery for bafetinib may be worthy of further investigation.

In this study we assessed bafetinib concentrations in both peritumoral and enhancing brain tissue and determined that the average brain ECF: plasma bafetinib ratio in patients is likely to be $< 0.05\%$. Studies in rats have suggested that bafetinib levels in the brain are approximately 10% of systemic levels.^{15,16} Since plasma protein binding of bafetinib in both humans and rats is 95%,²⁴ the apparent species-related difference in CNS penetration cannot be explained by differences in the availability of free drug. Assuming a free drug fraction of 5% in patient plasma, a fractional recovery of 85%, and equilibration of free drug across the BBB, we would expect to measure bafetinib levels in brain ECF in the range of 1-10 ng/ml, which would have been easily detectable by our method (LOD = 0.1 ng/ml).

Interspecies differences do exist regarding BBB permeability, and the observed discrepancy in brain uptake of bafetinib between rodents and humans could be due to dissimilarities in levels of expression, and substrate specificity of various efflux transporters, and/or BBB structural differences.²⁵⁻²⁷ In addition, the radiometric method used in the rats¹⁵ can overestimate drug levels in the brain due to the presence of residual blood in the tissue sample. The results of this study highlight the inadequacy of extrapolating data about CNS drug penetration from animal models to humans. Intracerebral microdialysis, which directly measures drug concentrations, is a preferred method for determining whether a drug can achieve therapeutic levels in the human brain.

Prior to performing intracerebral microdialysis in patients, *in vitro* studies must be done to assess a drug's fractional recovery and determine the optimal conditions for *in vivo* recovery. Nonetheless, *in vitro* recovery may overestimate *in vivo* recovery because the experimental set up cannot simulate conditions that affect *in vivo* recovery.²⁸ Several methods exist^{28,29} for *in vivo* catheter calibration, of which retrodialysis³⁰ is the most simple and direct. However, because bafetinib is not available as an intravenous formulation, it was not feasible to perform retrodialysis in our study patients.

Not all anti-cancer agents are amenable to microdialysis. Factors that limit a drug's recovery include high molecular weight, aqueous insolubility, and lipophilicity. In addition, microdialysis provides information only about drug levels within the vicinity of the catheter. Since tissues can be heterogeneous, the levels may not reflect drug concentrations throughout the tumor.

Despite these methodological concerns, use of microdialysis to perform neuropharmacokinetic assessments is growing.^{21,31,32} We have previously applied this technique to describe changes in intracerebral levels of temozolomide,²¹ a drug whose ability to cross the BBB is well established. In that study, we demonstrated that the time course of temozolomide concentrations in brain interstitium was not the same as in plasma,

which may have implications for the optimal timing of radiation when combined with temozolomide.

In this current study, we were able to conclude with only 6 patients that bafetinib does not achieve adequate concentrations in brain interstitium. In comparison, it required over 700 patients, within the context of multiple phase II trials³³⁻³⁷ as well as a phase III trial,³⁸ to determine that imatinib had minimal activity against high-grade gliomas. While it is unclear whether imatinib lacked efficacy because of its inability to reach tumor in the brain, like bafetinib, the drug is highly protein-bound and a substrate for efflux transporters. Two studies^{7,12} reported detectable imatinib levels in post-treatment tumor samples; however, as previously discussed, tissue-based measurements may over-estimate CNS penetration due to the contribution of residual blood in the specimen. Moreover, tissue measurements can only give information about intratumoral drug levels at one timepoint, whereas microdialysis can provide information about the time course of changes in drug levels in the brain.

This neuropharmacokinetic study of bafetinib illustrates the valuable role intracerebral microdialysis can play in early drug development. Such studies can be done within the context of standard cancer treatment—while patients are undergoing a craniotomy or brain biopsy. Although intracerebral microdialysis must take place in the hospital, collection of dialysate samples is done in ambulatory patients while recovering from surgery, often without prolonging hospitalization. Since only a small number of participants are needed, these studies can be performed relatively inexpensively and quickly. Lead-in microdialysis studies, such as the one described here, should be considered to assess the neuropharmacokinetics of a drug at its established maximum tolerated dose prior to initiating efficacy studies in brain tumor patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A.

Figure 1.

Fused images of a non-contrast head CT scan and a T1 post-contrast brain MRI of a study patient who underwent a gross total resection of tumor in the left frontal lobe. The CT scan was performed after the catheter was inserted to confirm correct placement of the catheter, and the MRI was performed on post-operative day 1. Images were autoregistered with mutual information matching algorithm using Varian Eclipse version 10.0 treatment planning system. The blended image is shown. A gold filament at the tip of the microdialysis catheter (arrow) is visible as bright signal on the CT scan but not visible on the T1 post-contrast MRI. Fused CT and T1 post-contrast MRI shows that the tip of the microdialysis catheter is placed in non-enhancing brain.

B.

Figure 1.

Fused images of a non-contrast head CT scan and a T1 post-contrast brain MRI of a study patient who underwent a biopsy of tumor in the right parietal lobe. The CT scan was performed after the catheter was inserted to confirm correct placement of the catheter, and the MRI was performed on post-operative day 1. Images were autoregistered with mutual information matching algorithm using Varian Eclipse version 10.0 treatment planning system. The blended image shows the gold filament of the catheter tip (arrow) as bright signal adjacent to enhancing brain tissue. The 3 mm gold tip is anterior to the 10 mm semi-permeable membrane (not visible on CT scan or MRI), which is in enhancing brain tissue.

Figure 2.
Plot of the bafetinib plasma concentration versus time following the first 2 oral doses taken 12 hours apart. Solid circles are the mean concentrations at each time point, and the error bars are the standard deviations.

Table 1

Patient characteristics

Patient	Age (years)	Gender	Diagnosis	KPS	Prior Chemotherapy	Surgical Procedure
1	68	Male	GBM	70	TMZ ^b , gene therapy study	Biopsy
2	37	Male	GBM	60	TMZ, isotretinoin, bev ^c , carboplatin	Resection
3	38	Female	PXA ^a with malignant features	70	TMZ	Resection
4	30	Female	Anaplastic astrocytoma	90	TMZ, carboplatin, etoposide,	Resection
5	27	Female	GBM	80	TMZ, bev	Biopsy
6	31	Male	Anaplastic oligoastrocytoma	80	carmustine wafer, TMZ	Biopsy

^aPXA = pleomorphic xanthoastrocytoma. Although PXA is classified as a grade II glioma by the World Health Organization, when this patient's tumor recurred, it had anaplastic features consistent with a higher grade glioma, and so she was eligible to participate in the study.

^bTMZ = temozolomide

^cbev = bevacizumab

Table 2

Plasma pharmacokinetics of bafetinib

Patient	Dose #1				Dose #2		
	Dose (mg)	Cmax (ng/ml)	Tmax (hr)	AUC 0-12h (ng/ml × hr)	Cmax (ng/ml)	Tmax (hr)	AUC 0-12h (ng/ml × hr)
1	240	112	4	623	235	3	921
2	240	237	2	873	183	3	585
3	240	65	8	374	340	4	1151
4	240	285	4	1396	231	8	1224
5	240	32	12	169	330	8	2164
6	360	129	3	522	164	4	1000
AVG =		143	6	660	247	5	1174
SD =		99	4	431	73	2	534