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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 peritumoural or enhancing brain tissue of seven patients at the time of tumour resection or biopsy. Twenty-four hours later, bafetinib was administered, 240 or 360 mg po, repeating the same dose 12 h later. Dialysate samples were continuously collected for 24 h, 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 tumour response.
Results: Twenty-six dialysate samples per patient were collected ($n = 6$) and analysed for bafetinib by tandem mass spectrometry. Bafetinib concentrations in the brain were below the lower limit of detection of the assay (0.1 ng/ml) in all samples except one 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 one patient remained on treatment past two 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

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drug as a treatment for brain tumours. 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.

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 leukaemia. In addition to inhibiting autophosphorylation of ABL point mutations, this dual TKI selectively inactivates Lyn[3] 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 tumour invasion and survival in glioblastoma.[5] *In vitro* studies of bafetinb 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 imatinib[7–12] 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 the rat brain were approximately 10% of plasma levels.[15,16] In mice, peak bafetinib concentrations in the brain occurred 2 h after oral administration, achieving concentrations above the IC50 for leukaemic 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 tumours, 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 analysed 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 $\geqslant$18 years old, have radiographic findings consistent with recurrent high-grade glioma, and be in need of tumour resection or biopsy. Other inclusion criteria were: (a) Karnofsky performance status (KPS) $\geqslant$60%, (b) recovery from toxicity of prior therapy, (c) adequate bone marrow function (absolute neutrophil count $\geqslant$1500 cells/mm^3 and platelet count $\geqslant$100,000 cells/mm^3), hepatic function (total bilirubin $\leqslant$2.0 mg/dL, serum levels of aspartate aminotransferase and alanine aminotransferase $\leqslant 3\times$ the institutional upper limit of normal), and renal function (serum creatinine $\leqslant 1.5\times$ 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 ms on electrocardiogram.

Patients were excluded from study participation if they (a) were taking hepatic enzyme-inducing anticonvulsants within 2 weeks prior to enrolment, (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 the frozen section indicated the presence of recurrent tumour, the neurosurgeon inserted a microdialysis catheter (70 Brain Microdialysis Catheter, M Dialysis, Solna, Sweden) into residual tumour or peritumoural tissue within 5–15 mm of the resection cavity. After a post-operative non-contrast computerised 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 μL/min. Contrast-enhanced brain magnetic resonance images (MRIs) were obtained within 24 h of surgery to serve