Evaluation of the effects of the triple angiokinase inhibitor BIBF 1120 on tumor vasculature in a phase I clinical trial using Dynamic Contrast-Enhanced MRI (DCE-MRI)

R. Strecker[1], K. Mross[2], M. Stefanic[3], L. de Rossi[3], J. Hennig[1]

[1]MRDAC, University Hospital, Freiburg, Germany, [2]Tumorbiology Center, Freiburg, Germany, [3]Boehringer-Ingelheim Pharma GmbH & CO KG, Biberach, Germany

Introduction

BIBF1120 is a potent, orally available triple angiokinase inhibitor (VEGFRs, PDGFRs, FGFRs). The primary objective of this Phase I dose escalation study was to determine the maximum tolerated dose (MTD) of BIBF 1120 in patients with solid tumors. Secondary objectives were the evaluation of safety, efficacy, pharmacokinetics and pharmacodynamic effects of BIBF 1120. DCE-MRI was measured to explore the effects of BIBF1120 on tumor microcirculation.

Materials and Methods

BIBF 1120 was first escalated with once daily dosing (qd) until dose limiting toxicity (DLT; MTD: 250 mg qd) was observed. In a second cohort, twice daily dosing (bid) was explored to further increase drug exposure (MTD: 250 mg bid). DCE-MRI was performed at baseline, day1/2 after first oral dosing and at the end of every 28 day cycle.

DCE-MRI was acquired using an inversion recovery trueFISP sequence with a high temporal resolution of 3s [1]. The use of a balanced SSFP readout provides high contrast between tumor and healthy tissue for accurate placement of region of interest (ROI) for data analysis. The ROI was defined circumscribing the whole tumor. iAUC (initial area under Gd concentration time curve for first 60s) and K^{trans} were derived by whole ROI as well as pixelwise analysis applying the Tofts model with a standard vascular input function.

Slice thickness was 10mm and inplane resolution was 3.1mm. The imaging slice was positioned in a coronal oriented plane cutting through the center of the tumor in order to correct for spatial displacement of lesion during breathing. Collection of 110 time points resulted in a total acquisition time of 5,5min. A single dose of Gd-DTPA was administered with an injection rate of 2 ml/s using a power injector.

61 patients with tumors/metastasis in lung, liver and other abdominal sites were enrolled in the study. 59 patients received more than one MRI examination and were considered for DCE-MRI analysis. 7 pts. were excluded from DCE-MRI analysis due to following reasons: image artifacts i.e. pulsation, extensive through-plane motion caused by arrhythmic breathing or absence of contrast uptake. 45/59 patients completed cycle 1 with an evaluable DCE-MRI examination. 22/59 received at least three treatment courses. Tumor response was defined as a minimum change of -40% in iAUC from baseline.

Results

BIBF 1120 showed a favorable safety profile at doses up to 250 mg qd and 250 mg bid. The median time to tumor progression for all patients receiving once daily BIBF 1120 was 99 (range: 64-145) days and 106 (range: 64-172) days in patients receiving twice daily BIBF 1120. About 60% of all patients presented clinically stable tumor disease over at least two treatment courses. One patient showed a complete clinical response at 200mg BIBF 1120 qd and 2 patients showed a partial response of their tumor disease at 250mg BIBF 1120 bid and 300mg BIBF 1120 bid respectively.

A decrease of ≥ 40% in iAUC60 was observed in 8/45 patients at the end of cycle 1. Respective numbers for K^{trans} were 12/45 evaluable patients. The maximum number of responders in total is found at the end of course 2 (11/35 evaluable patients). Most of the responders were treated with doses in the range of 250-300mg qd and 250mg BIBF 1120 bid (Fig. 1). K^{trans} maps of a patient with a liver metastasis treated with 150mg BIBF 1120 bid are demonstrated in Fig. 2. The corresponding K^{trans} time profiles (median of ROI) demonstrate an objective response by a decrease >40% at the end of cycle 2 and subsequently (Fig. 3).

No statistical significant correlation between the reduction in iAUC60 and K^{trans} at the end of cycle1 and objective clinical response was observed. High inter-individual differences in plasma concentrations of BIBF 1120 with a strong overlap between different dose groups were detected. A statistically significant dose dependency of iAUC or K^{trans} could not be observed. Most of the responders were patients with a liver metastasis as target lesion.

Discussion

The results indicate that tumor patients may benefit from treatment with BIBF 1120 by inhibition of tumor progression and reduction of tumor size. DCE-MRI results suggest an antiangiogenic effect of BIBF 1120 without a significant dose dependency as compared to studies with different antiangiogenic compounds [2]. A reason might be the heterogeneous patient cohorts with different primary tumor types since almost all responses were measured in liver metastasis. BIBF 1120 is a promising compound that warrants further clinical investigation.

References

(1) Strecker ISMRM 2004

(2) Morgan B, et. al. *J Clin Oncol.* 2003 Nov; 21(21): 3955-64.

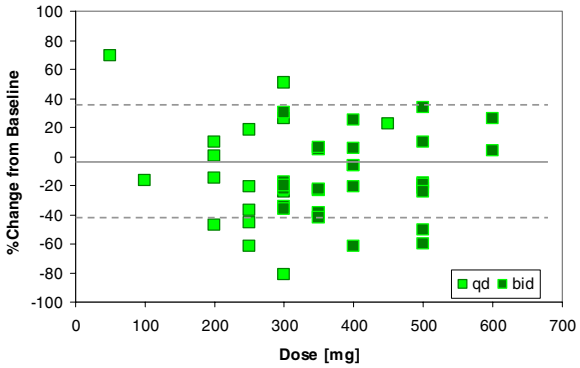

Figure 1: Percentage change of median iAUC in tumor at day28. Value for patient 57 (500mg) is not displayed (ΔAUC= 179,8%).

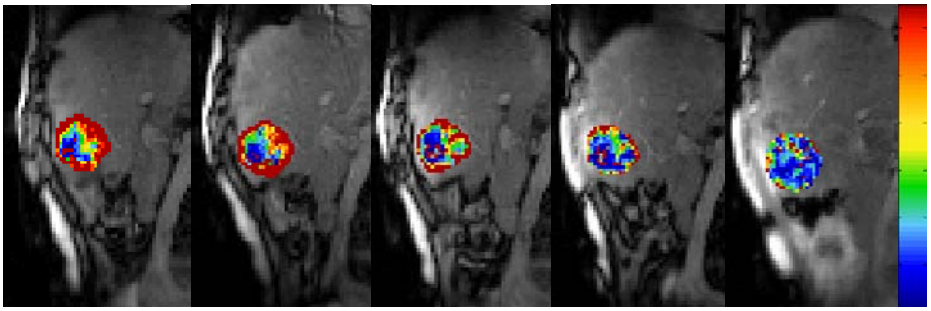

Figure 2: K^{trans} maps from a patient with liver metastasis registered to native trueFISP images. A) pre-treatment, B) day 2, C) day 28, D) day 56 and E) day84 after start of treatment. (Patient 26, treated with 2x150mg BIBF 1120 per day).

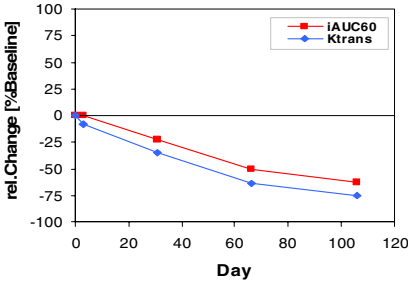

Figure 3: Median K^{trans} and iAUC values from patient 26. A continuous decrease with increasing treatment duration is observed.