Short-term treatment with the triple angiokinase inhibitor, BIBF 1120, affects vascular permeability and perfusion of human tumor xenografts in nude mice.

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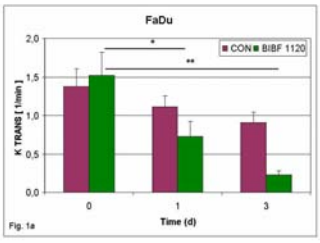
Introduction: Tumor angiogenesis plays an essential role in the progression of human malignancies. BIBF 1120, a potent and selective, orally available "triple angiokinase inhibitor" targeting VEGFRs, PDGFRs, and FGFRs is currently in clinical development for treatment of solid tumors. BIBF 1120 induces apoptosis in endothelial cells and exhibits excellent single-agent anti-tumor activity in multiple preclinical tumor models [1]. This study was designed to assess the effects of short-term treatment with BIBF 1120 on tumor vasculature and its function in subcutaneous human tumor xenograft models.

Methods: Nude mice bearing established subcutaneous head and neck carcinoma (FaDu, n=7; 100-250 mm^3) and colon carcinoma (HT-29, n= 8; 70-240 mm^3) tumors were treated with daily oral doses of BIBF 1120 (100 mg/kg) for three consecutive days. Untreated tumor-bearing mice (n=8 for both tumor models) served as controls. Tumor volume and vasculature were assessed before, 24 and 72 hours after treatment initiation.

All experiments were performed in a PharmaScan 70/16 MR System (Bruker Biospin, Germany) using 38 mm ^{1}H volume resonator. Tumor volume was measured from Multi-slice Spin Echo images (TE= 30 ms, TR= 1s) of the tumor region. Tumor perfusion and permeability were determined by dynamic contrast enhanced (DCE) MRI using Gd-DTPA (0.1 mmol/kg,; single slice 2D T1w FLASH, flip angle 30°, TE= 2.8 ms, TR= 13.5 ms). Toft´s model analysis [2] was used to assess the transfer constant (K^{TRANS}) as implemented in Jim 3.0 Image Analysis software package (Xinapse Systems Ltd. UK). Predefined arterial input function was extracted from series of calibration measurements. Relative blood volume (rBV) was determined from signal enhancement (ln S/S_0) in T1w FLASH images after a bolus (0.016 mmol/kg) of macro-molecular gadolinium-based contrast agent P792 (Vistarem™, Guerbet, France) [3]. Data are given as mean ± SEM. Repeated measures (RM) ANOVA was used to estimate the effect of treatment on time course of measured variables.

Results: In FaDu tumor xenografts, similar tumor volumes, K^{TRANS} and rBV were determined in both groups prior to treatment. Tumor growth was not affected by 3 days of treatment with BIBF 1120. By contrast, 3 days of treatment with BIBF 1120 reduced K^{TRANS} value by 80% ($p<0.01$ vs. pretreatment), resulting in ~75% lower K^{TRANS} ($p<0.05$) values compared with control tumors on day 3 (Fig. 1a). BIBF 1120 treatment also reduced rBV by ~55% ($p< 0.05$ vs. pretreatment) (Fig 1b).

There was no difference in tumor volumes, K^{TRANS} and rBV in the HT-29 tumor-bearing groups prior to treatment. Interestingly, K^{TRANS} and rBV values in untreated HT-29 xenografts were lower (K^{TRANS}: ~15%, rBV: ~50%, $p<0.01$) than those in FaDu tumors, indicating a lower grade of tumor perfusion and vascular permeability. Tumor growth was again not affected by three days of treatment with BIBF 1120, but K^{TRANS} values were reduced by ~40% ($p=0.095$ vs. pretreatment), resulting in about ~50% lower K^{TRANS} ($p=0.084$) values compared with control tumors on day 3 (Fig 2a). BIBF 1120 treatment also reduced rBV by ~40% ($p< 0.01$ vs. pretreatment) (Fig 2b).



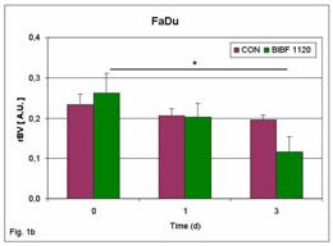
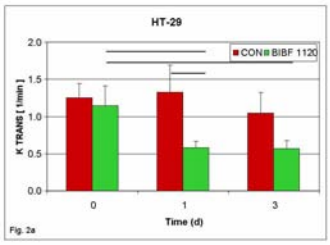


Fig.1. Effect of BIBF 1120 on K^{TRANS} (a) and rBV (b) in the FaDu model.



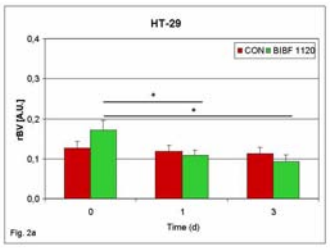


Fig.2. Effect of BIBF 1120 on K^{TRANS} (a) and rBV (b) in the HT-29 model.

Black lines denote significant differences.

Conclusion: BIBF 1120 treatment has a significant impact on the tumor vasculature in both models, resulting in a substantial decrease in tumor perfusion and vascular permeability. These changes can be detected by DCE-MRI prior to changes in tumor growth rate.

References: **[1]** Hilberg F. et al. 16th AACR-NCI-EORTC Symposium on „Molecular Targets and Cancer Therapeutics", Poster #158, 2004; **[2]** Tofts, P.S. et al. J Magn Reson 10: 223, 1999; **[3]** Port M. et al. MAGMA 12:121, 2001