

Dynamic MRI evaluation of the triple receptor tyrosine kinase inhibitor BIBF 1120 in patients with advanced solid tumours

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BIBF 1120 is a potent inhibitor of the Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2) tyrosine kinase. In vitro, the tyrosine kinase receptors (TKR) of VEGFR-1&3, FGF Receptor 1&3, and PDGF Receptor- α (PDGFR- α) are inhibited as well. Dynamic contrast enhanced MRI (DCE-MRI) is now used in many phase I clinical studies of antiangiogenesis agents as a pharmacodynamic indicator of the success of therapy and the information provided can be used to identify a biologically active dose to take into efficacy studies [1]. Here we report on the antivascular activity of BIBF 1120 demonstrated by DCE-MRI performed in the 1st cycle of treatment in a phase I clinical study.

Methods: 35 consecutive patients entering into a 2 centre antiangiogenesis study were examined. All patients had failed conventional therapy and received oral BIBF 1120 in escalating doses. Both centres used similar hardware (1.5T Siemens systems) and protocols: T₁ weighted dynamic scans (three 8mm slices, TE 4.7ms, TR 11ms, α 30°) with a proton density reference image (TR 20 or 31ms, α 30°, rest as T1W) and 0.1mmol/kg Gd-DTPA injected at 4ml/s. The quality assurance and quality control procedures were identical for the 2 centres. Regions of interest were drawn by 2 experienced observers working independently using MRIW software (ICR, London) using the pharmacokinetic model of Tofts[2] with the vascular input function described by Fritz-Hansen[3]. Examinations were performed twice pre-treatment (to estimate reproducibility) and after 24 hours and 28 days of treatment (to assess response) in the 1st cycle of treatment. Kinetic parameters related to tumour perfusion and permeability were obtained; transfer constant (K^{trans}), rate constant (k_{ep}) and initial area under gadolinium curve at 60 seconds (IAUGC₆₀) and changes compared in individual and group analyses according to the drug dose received using the 95% confidence interval for change estimated from the reproducibility analysis.

Results: Individual patient analyses showed that some patients had significant reductions in all kinetic parameters (particularly k_{ep}) consistent with antiangiogenesis effects at both the 24hr and 28d time points in the 1st cycle of treatment but the majority did not (Fig 1).

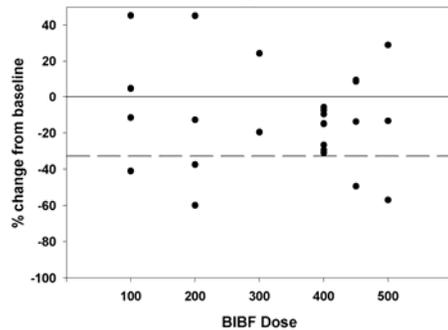


Fig 1. Individual patient effects on k_{ep} by drug dose. The lower control line indicates the 95% CI of repeatability (r) for one patient ($r\% = -32.7\%$ to $+48.5\%$). The same data are shown as dose cohorts in Fig 2

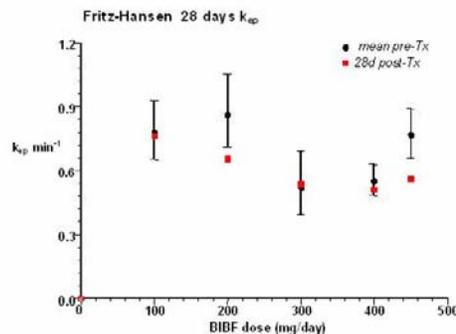


Fig 2. Dose cohort effects on k_{ep} . The raw data are shown in Fig 1. The circle indicates the mean pre-treatment k_{ep} for each cohort and the square the change with therapy at 28 days. 95% CI for significance are shown.

Statistically significant reductions were also seen in 3/27 patients in IAUGC₆₀ and in 2/27 patients in K^{trans} at 28d. Group analysis showed statistically significant reductions in all kinetic parameters at doses of 200mg and >400mg/day (Fig 2). The greatest reductions in kinetic parameters were seen in patients with metastatic liver disease. No patients had significant reductions in tumour size as defined by the WHO criteria.

Discussion: DCE-MRI is able to show antiangiogenesis effects of BIBF 1120 in the setting of a phase I clinical trial in

the 1st cycle of treatment. We did not show definite drug dose dependence although the best results were obtained with the higher doses. The clearest results occur in the k_{ep} parameter which is a measure of permeability and in patients with liver metastases. The lack of a large DCE-MRI effect may be due to the opposing effects on vascular permeability caused by VEGF inhibition (reduces permeability) and PDGF inhibition (increases permeability) or because we only evaluated patients in the 1st cycle of therapy. The need to perform drug dose cohort analysis and to gauge the significance of changes against the reproducibility of the DCE-MRI technique is emphasised.

References:

- [1] Leach MO *et al.*, *Br J Cancer* 2005;**92**(9):1599-1610
- [2] Tofts, P.S. and Kermode, A.G. *Magn Reson Med.* 1991; **17**: 357
- [3] Fritz-Hansen T. *et al.*, *Magn Reson Med.* 1996 Aug; **36**(2): 225-31