Vascular response of hepatocellular carcinoma to pazopanib measured by Dynamic Contrast-Enhanced MRI: pharmacokinetic and clinical activity correlations

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Introduction

DCE-MRI has been incorporated widely to support the clinical development of vasculature-targeting agents. However, only a limited number of DCE-MRI studies have been performed for dose-ranging applications that correlate PK, DCE-MRI-derived parameters, and clinical activity [1-3]. Here a Phase I, dose-ranging study of pazopanib in a defined HCC population has been performed with DCE-MRI on a subset of subjects.

Methods

A Phase I study of pazopanib was conducted in patients with locally unresectable or advanced HCC to determine the maximum tolerated dose (MTD) as well as to evaluate safety, PK, clinical activity and vascular response using DCE-MRI. The study was conducted across 3 centres, with 2 centres contributing imaging data. Eligibility criteria included HCC with at least one target lesion, recovery from prior therapy, ECOG performance status 0 or 1, Child-Pugh A, and adequate organ function. Pazopanib was escalated from 200 to 800mg/day. DCE-MRI was performed to determine K^{trans} (endothelial transfer coefficient) and $IAUC_{60}$ (initial area under the contrast agent-time course for the first 60s post contrast) at baseline and day 22. Pazopanib PK, including C24, Cmax and Tmax was determined at steady state on Day 15 of Cycle 1.

Results

17 of 28 patients treated with doses of either 200mg (n=4), 400mg (n=5), 600mg (n=5) or 800mg (n=3) successfully completed both baseline and day 22 DCE-MRI acquisitions. Median (range) values for % change in $IAUC_{60}$ in order of increasing doses from 200-800mg were: -17.3(-11.7,-24.7), -15.9(30.3, -47.9), -39.6(12.6, -56), -59.9(10.8,-78.4). For %change in K^{trans} the median (range) values were: -36.25(-22.9, -70.0), -23.0(-9.5, -76.8), -44.6(9.2, -45.6), -73.8 (-37.5, -86.2). The greatest reductions in K^{trans} and $IAUC_{60}$ were demonstrated at the largest doses of pazopanib, although significant vascular changes were measured at lower doses. A weak association was observed between %change in $IAUC_{60}$ and Cmax [correlation coefficient $\rho=0.47$] although this was stronger than the association between $IAUC_{60}$ and dose [correlation coefficient $\rho=0.30$]. DCE-MRI changes versus Tmax (time to peak drug concentration) demonstrated that significant reductions in $IAUC_{60}$ were associated with a Tmax of 2 hours or less. Furthermore, in a similar approach to previous analyses by Zhu *et al.*, [4] the ratio of day 22 to baseline K^{trans} was analysed for subjects categorised by clinical response, defined as those subjects achieving either a partial response or stable disease for 4 months or subjects defined as having progressive disease within 4 months. No statistically significant difference was identified between the two groups.
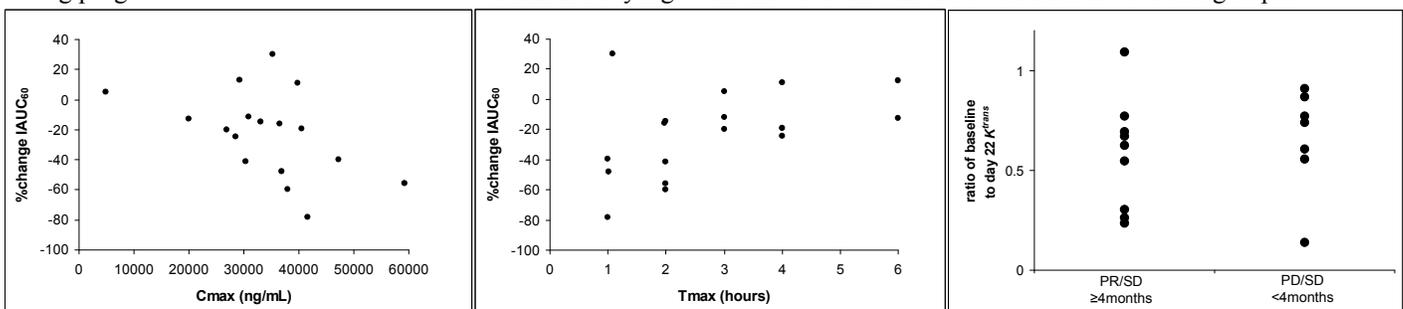
Left: %change in DCE-MRI derived $IAUC_{60}$ following 22 days of pazopanib versus Cmax (maximum concentration) derived from 15 day PK data. **Middle:** %change in $IAUC_{60}$ versus Tmax. **Right:** ratio of baseline to day 22 K^{trans} for patients categorised by clinical response: PR/SD≥4 months (n=10) and PD/SD<4 months (n=7).

Discussion

Relationships were identified between DCE-MRI parameters and individual PK parameters of pazopanib. Given that relationships between dose and peak concentration and systemic drug exposure are often complex, it is likely that the prescribed dose alone will not account for patient-specific differences in exposure to pazopanib by the tumour. Studying PK relationships with DCE-MRI data may be more informative than relying upon dose alone. The estimated correlations between %change in $IAUC_{60}$ and Cmax and Tmax suggest that the greatest change to the vasculature occurs when the rate of drug absorption is rapid. No relationship was identified between the two categories of clinical response defined. Correlations between pharmacodynamic endpoints and clinical response in this study setting are likely to be complex. However, these data suggest that DCE-MRI responses are largely dominated by pharmacokinetic factors. DCE-MRI continues to play an important role in providing a pharmacodynamic read-out of vasculature-targeting agents, enabling different drug doses and patient-specific PK factors to be studied.

References

[1] Liu *et al.*, J. Clin. Oncol., 23(24), 5464-5473, 2005.
[2] Thomas *et al.*, J. Clin.Oncol., 23(18), 4162-4171, 2005.
[3] O'Connor *et al.*, Br. J. Cancer, 96, 189-195, 2007.
[4] Zhu *et al.*, J. Clin. Oncol., 27(18), 3027-3035, 2009.