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A Phase 1 dose-finding and pharmacodynamic study of rapamycin in combination with bevacizumab in patients with unresectable hepatocellular carcinoma

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Abstract ***Background & Aims:*** Preclinical studies have demonstrated the additive effect of rapamycin with bevacizumab for hepatocellular carcinoma treatment. We conducted a Phase 1 study to evaluate the safety and pharmacokinetics of the combination in patients with hepatocellular carcinoma.

Methods: Adult participants with advanced hepatocellular carcinoma received intravenous bevacizumab (5 mg/kg every 14 days) and oral rapamycin (1–6 mg/day; 3 + 3 dose escalation design). Computed tomography assessed tumour response and treatment safety. Pharmacokinetics assessment established rapamycin blood concentrations pre- and post-dose. Dynamic contrast-enhanced computed tomography analysed the tumour region for blood flow, permeability surface area product, fractional intravascular blood volume and extracellular–extravascular volume.

Results: Twenty-four participants were treated. There were two dose limiting toxicities with rapamycin 5 mg: grade 3 thrombocytopenia and grade 3 mucositis. The maximally tolerated dose of rapamycin was 4 mg. Adverse events (grade 1–2) included hyperglycaemia (83%), thrombocytopenia (75%), fatigue (46%), mucositis (46%), anorexia (42%), diarrhoea (33%) and proteinuria (12.5%).

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Of 20 evaluable participants, one reached complete response that lasted 4.5 months, two reached partial response, 14 reached stable disease and three had progressive disease. Median overall survival was 9.4 months; progression-free survival was 5.5 months.
Dose level and steady state area under the concentration time curve for hour zero to infinity of rapamycin correlated inversely with blood flow rate and change in permeability-surface area. After 22 days of treatment, there were significant reductions from baseline in blood flow rate, permeability-surface area and fractional intracellular blood volume.
Conclusions: The recommended Phase 2 dose of rapamycin is 4 mg in combination with bevacizumab. Evidence of anti-vascular activity was observed together with promising clinical activity.

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common cancer in East Asian males and the third leading cause of cancer mortality worldwide [1].

Bevacizumab, a humanised monoclonal antibody against human vascular endothelial growth factor (VEGF), has shown activity (as a single agent and in combination with chemotherapy), yielding response rates of up to 20% and a median survival of up to 12.4 months in HCC [2,3].

The mammalian target of the rapamycin pathway (mTOR) is activated in 40–50% of HCC patients and its inhibition by rapamycin affects tumour growth and angiogenesis [4,5]. A study of 24 advanced HCC patients found that with rapamycin dosed to maintain the trough level at 10–15 μg/L, one patient had partial response and five had stable disease after 3 months [6]. A study of 24 advanced HCC patients found that rapamycin given at 30 mg weekly resulted in one complete response, one partial response and eight patients with stable disease [7]. Median survival was 26.4 weeks.

Our group previously showed that the combination of bevacizumab and rapamycin exhibited additive tumour inhibitory effect in HCC xenograft models compared to either agent alone. Pharmacodynamic analysis revealed reductions in VEGF expression, cyclin D1 and cyclin B1 [8–10]. Based on these findings, we embarked on a Phase 1 study to evaluate the safety and pharmacokinetics of rapamycin in combination with bevacizumab in advanced HCC.

2. Patients and methods

2.1. Participant enrolment

This study enrolled patients who were $\geqslant$18-years-old; had histologically-confirmed measurable, unresectable HCC not amenable to local therapy; a Child-Pugh score of A or B; an Eastern Cooperative Oncology Group performance status (ECOG) $\leqslant$2; an absolute neutrophil count $\geqslant 1.5 \times 10^9$/L; platelets $\geqslant 100 \times 10^9$/L; creatinine within normal limits; bilirubin $\leqslant 3 \times$ upper limit of normal (ULN); aspartate aminotransferase/alanine aminotransferase $\leqslant 5 \times$ ULN; a fasting serum cholesterol $\leqslant$9 mmol/L; triglycerides $\leqslant$3.39 mmol/L; and had to be on anti-viral therapy for hepatitis B carriers. Exclusion criteria included the failure of $\geqslant$2 prior systemic therapies for HCC, proteinuria $\geqslant$2 or 24-h urine protein $>$1 g, a bleeding disorder, thromboembolic disease, long-term anticoagulation, a history of hemoptysis or hemetemesis, central nervous system metastases, known HIV infection or a life expectancy of $<$3 months.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the Singhealth Centralised institutional review board. Prior to enrolment, all participants gave written informed consent.

2.2. Study design and drug treatment

This was an investigator-initiated, open-label, single-arm Phase 1 trial which recruited patients based on a "3 + 3" dose-escalation design until the maximally tolerated dose (MTD) was achieved. MTD was defined as one dose level below that at which $\geqslant$2 participants experienced dose limiting toxicity (DLT). DLT was defined as grade 4 neutropenia of greater than 7 days, neutropenic fever, grade 4 anaemia, grades 3–4 thrombocytopenia, any grade 3–4 non-haematologic toxicity during the first 28 days of treatment, or any toxicity that causes a 14-day treatment delay. An expanded cohort of six participants was further recruited at the MTD level. No intra-patient dose escalation was allowed.

Oral rapamycin (Wyeth) was dosed daily at 1 mg at dose level 1, and was escalated in increments of 1 mg per dose level up to an allowable maximum dose of 6 mg at dose level 6. Intravenous bevacizumab (Roche) was given concurrently at a fixed dose of 5 mg/kg every 14 days. A 28-day treatment period comprised one cycle. The study only provided for up to six cycles of study drugs due to funding constraints. Patients were allowed to continue beyond six cycles if treatment was beneficial at their own cost. Otherwise, treatment was discontinued