A Phase II Study of Pazopanib in Asian Patients with Recurrent/Metastatic Nasopharyngeal Carcinoma

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Abstract

**Purpose:** Nasopharyngeal carcinoma is endemic in Asia and angiogenesis is important for growth and progression. We hypothesized that pazopanib would have antiangiogenic activity in nasopharyngeal carcinoma.

**Experimental Design:** A single arm monotherapy study of pazopanib in patients with WHO type II/III nasopharyngeal carcinoma who had metastatic/recurrent disease and failed at least one line of chemotherapy. A Simon’s optimal 2-stage design was used. Patients with Eastern Cooperative Oncology Group (ECOG) 0-2 and adequate organ function were treated with pazopanib 800 mg daily on a 21-day cycle. The primary endpoint was clinical benefit rate (CR/PR/SD) achieved after 12 weeks of treatment. Secondary endpoints included toxicity and progression-free survival. Exploratory studies of dynamic-contrast enhanced computed tomography (DCE-CT) paired with pharmacokinetics (PK) of pazopanib was done.

**Results:** Thirty-three patients were accrued. Patients were ECOG 0-1 with median age of 50 years (range 36–68). There were 2 (6.1%) partial responses, 16 (48.5%) stable disease, 11 (33.3%) progressive disease, 4 (12.1%) were not evaluable for response. The clinical benefit rate was 54.5% (95% CI: 38.0–70.2). Ten patients (30.3%) received more than 6 cycles (4 months) of treatment and 7 (21.2%) had PR/SD that lasted at least 6 months. One patient each died from epistaxis and myocardial infarction. Common grade 3/4 toxicities included fatigue (15.2%), hand-foot syndrome (15.2%), anorexia (9.1%), diarrhea (6.1%), and vomiting (6.1%). Serial DCE-CT scans show significant reductions in tumor blood flow, permeability surface area product, and fractional intravascular blood volume.

**Conclusion:** Pazopanib showed encouraging activity in heavily pretreated nasopharyngeal carcinoma with an acceptable toxicity profile. Clin Cancer Res; 17(16); 1–9. ©2011 AACR.

Introduction

Nasopharyngeal carcinoma is endemic in East and South-East Asia and Southern Chinese have the highest incidence of nasopharyngeal carcinoma (1). Endemic nasopharyngeal carcinoma are of WHO type II and III and is intimately associated with Epstein–Barr virus infection (2, 3). In high-risk populations it is a disease that afflicts a high proportion of young patients (<50 years) and is associated with excess disease and treatment related morbidity. Greater than 50% of patients will present with advanced nasopharyngeal carcinoma (metastatic or locally advanced recurrent disease; ref. 4, 5).

A feature of endemic nasopharyngeal carcinoma is its chemosensitivity. Initial chemotherapy for metastatic or locally recurrent disease with a platinum-containing chemotherapy regimen gives a response rate as high as 65%–75% (6, 7), with time to progression of about 7 months and a median survival of 11 months (8). With new generation cytotoxic agents, the disease remains fairly chemoresponsive in both first and second line settings with response rates ranging from 17% to 28% (8–11). However, the median progression-free survival (PFS) for patients who had at least one previous line of chemotherapy ranges from 3.9 months (11) to 5.1 months (10). Despite this the 5-year survival remains poor for metastatic disease or recurrent disease (5, 12). Clearly, there is a need to pursue new combinations and novel drugs to treat patients with metastatic and recurrent nasopharyngeal carcinoma.
Translational Relevance

Pazopanib is an antiangiogenic multitargeted tyrosine kinase inhibitor. Given the central importance of angiogenesis in solid tumors, including nasopharyngeal carcinoma, we conducted a phase II trial of pazopanib in this endemic disease where few targeted therapies have shown efficacy. Of 33 patients, all of whom were heavily pretreated, we found pazopanib monotherapy to have an acceptable safety profile, with clinical benefit in 54.5%, and 21.2% of patients achieving either stabilization of disease or response for at least 6 months. The pharmacokinetics of a daily dose of 800 mg once a day in this all Asian population shows that AUC_{0–24} were at least 20% higher than reported levels in Western populations at steady state. Dynamic contrast enhanced computed tomography measurements confirmed antiangiogenic activity of pazopanib. Paradoxically, patients who had greater reduction in tumor permeability after treatment were associated with worse outcomes.

Pazopanib is a potent and selective, orally available, small molecule inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor (PDGF)-α, PDGF-β, and c-kit tyrosine kinases. Nasopharyngeal carcinoma constitutes a plausible target for this drug as angiogenesis constitutes an important pathway for tumor growth in endemic nasopharyngeal carcinoma. LMP-1 induces COX2 expression that in turn upregulates VEGF expression in nasopharyngeal carcinoma cells (13). Initial studies that used angiogenesis inhibitors in nasopharyngeal carcinoma cell lines showed tumor inhibition in combination with 5-fluorouracil (14). High serum VEGF levels correlate with poorer prognosis and development of local recurrence and metastasis (15). Increased tumor microvessel density is also increased in tumors with local invasion and metastasis in association with an increase in VEGF expression (16). This increased angiogenic potential is also associated with lower overall survival (OS; refs. 16–18) in some studies. Overexpression of tumor VEGF is also reported in 60%–70% of nasopharyngeal carcinoma (19, 20). Coexpression of tumor VEGF and hypoxia-related growth factors in nasopharyngeal carcinoma are also associated with poorer prognosis (20). In a mouse nasopharyngeal carcinoma model developed in National Cancer Centre Singapore, addition of antiangiogenic agents potentiated the effects of photodynamic therapy in addition to having antitumor effects in themselves (21). Finally, a small phase I study of a VEGFR-1 inhibitor in solid tumors showed few minor responses in nasopharyngeal carcinoma patients (22).

We therefore hypothesized that pazopanib in endemic nasopharyngeal carcinoma would allow targeting of VEGFR and tumor neovascularization that is important for tumor growth and carcinogenesis. We also explored the use of dynamic-contrast enhanced computed tomography (DCE-CT) as a pharmacodynamic indicator of antiangiogenesis, taking into consideration interpatient variability in pharmacokinetics of pazopanib.

Materials and Methods

Patients

Patients enrolled on the study had histologically or cytologically confirmed recurrent or metastatic nasopharyngeal Carcinoma (WHO type II/III) and measurable disease, defined as at least 1 lesion accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥20 mm or more with conventional techniques or as ≥10 mm or more with spiral CT scan. Patients had failed at least 1 prior line of chemotherapy for metastatic or recurrent disease, age 18 or older, had life expectancy of more than 3 months, Eastern Cooperative Oncology Group (ECOG) performance status 2 or less (Karnofsky ≤ 60%), and normal organ and marrow function: leukocytes 3,000/mcL or more, absolute neutrophil count 1,500/mcL or more, platelets 100,000/mcL or more, liver and renal function within normal limits, PT/INR/PTT within 1.2× the upper limit of normal, blood pressure no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) before entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier were not eligible. Patients with greater than +1 proteinuria on 2 consecutive dipsticks taken at least 1 week apart, with QTc prolongation (defined as a QTc interval equal to or greater than 500 m/s) or other significant ECG abnormalities, poorly controlled hypertension (systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher) were ineligible. Patients with any condition (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs their ability to swallow and retain pazopanib tablets were excluded.

Patients with any of the following conditions were excluded: Serious or nonhealing wound, ulcer, or bone fracture, history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment, any history of cerebrovascular accident within the last 6 months, current use of therapeutic warfarin. Low molecular weight heparin and prophylactic low-dose warfarin were permitted so long as PT/PTT met the inclusion criteria. Patients with a history of myocardial infarction, cardiac arrhythmia, admission for unstable angina, cardiac angioplasty or stenting within the last 12 weeks, history of venous thrombosis in last 12 weeks and class II or IV heart failure as defined by the NYHA functional classification system were excluded. Patients with known brain metastases and uncontrolled intercurrent illness including, but not limited to, ongoing


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or active infection or psychiatric illness/social situations that would limit compliance with study requirements were excluded. Patients with known allergy to CT contrast agents were excluded.

**Treatment schedule**

This was a monotherapy study of pazopanib at a daily dose of 800 mg. Patients were instructed to take the drug at least 1 hour prior to meal or 2 hours postmeal with 300 mL of water to ensure optimal absorption. Patients were given home blood pressure sets and a diary to document their daily blood pressure and compliance.

**DCE-CT studies**

DCE-CT is a noninvasive method of measuring the tumor vasculature, and has been correlated with histologic markers of angiogenesis in cancer (23–26). Different vascular parameters can be measured by use of DCE-CT depending on the physiologic and mathematical algorithm applied. The distributed parameter (DP) tracer kinetic model provides measurements of tumor blood flow and permeability separately by modeling each of these processes explicitly within the vascular and interstitial compartments of the tumor (27). Blood flow derived from the DP model has been validated against H215O-positron emission tomography imaging in patients with acute stroke (28), while permeability has been validated in vitro against hollow fiber bioreactors.

A 64-detector row CT scanner (Lightspeed; General Electric) was used. A 20 G cannula was set at the antecubital fossa. After a pilot scan, a 4 cm slab was placed over the selected lesion with the following settings: 8 slices at 5 mm collimation, 100 kV, 80 mAs, Field of View 50 × 50 cm, Matrix 512 × 512; and a precontrast slab was acquired. Subsequently, 70 mL of nonionic iodinated contrast (Omnipaque 300) was administered at 4 mL per second with a power injector followed by 30 mL of saline at the same rate. The dynamic scans comprised of 26 acquisitions at increasing time intervals (11 scans at 2 seconds, 7 scans at 4 seconds, 1 scan at 8 seconds and 7 scans at 12 seconds) over the same table position, done after a delay of 8 seconds from the start of contrast injection.

A region of interest (ROI) was drawn to include the tumor. One dominant lesion was selected per patient. Manual image coregistration was done to correct for respiratory motion. The ROIs were copied onto each selected slice corresponding to each time point. The ROIs on each slice were manually displaced to best account for respiratory difference between slices. The size and shape of each ROI were not changed. The arterial input function (AIF) was obtained by averaging the CT numbers (in Hounsfield Units, HU) within an ROI drawn over the aorta or a major artery.

Concentration-time curves corresponding to each voxel within the tumor ROI were individually fitted using the DP model and the sampled AIF, and parameter maps of the tumor were generated. Median values of the various parameters corresponding to the tumor voxels were obtained. The following parameters were analyzed: blood flow (F; mL/100 mL/min), permeability surface area product (PS; mL/100 mL/min), fractional intravascular blood volume (v1; mL/100 mL), and extracellular-extravascular volume (v2; mL/100 mL). Computation of these parameters and the generation of the corresponding parametric maps were done using Matlab (MathWorks).

Paired DCE-CT scans were done with a minimum interval of 24 hours between the scans to establish reproducibility, together with an additional scan 28 days after starting treatment with pazopanib to assess tumor vascular changes. Paired t test was done to compare mean changes before and after treatment. Spearman correlation was done to correlate changes in DCE-CT parameters to pharmacokinetic measurements. Receiver operator curve (ROC) analysis was done, using the nonparametric assumption, and the null hypothesis that the true area under the curve (AUC) is 0.5, to compare changes in DCE-CT measurements between patients who had progressive disease with those who had responded to treatment or had stable disease. Cut-offs with optimal sensitivity and specificity were defined, and used to obtain Kaplan–Meier survival curves. Log-rank test was done to compare the change in DCE-CT parameters to progression-free survival.

Bland–Altman reproducibility statistics were used to estimate measurement (29).

Reproducibility analysis based on the Bland–Altman 95% limits of agreement has been reported. The 95% limits of change for a group of "n" patients can be estimated from the value of the mean squared differences (dSD) derived from the reproducibility data set using the following formula: (1.96 × dSD)/On. The dSD values for F, PS, v1, and v2 are 10.4 mL/100 mL/min, 9.3 mL/100 mL/min, 3.1 mL/100 mL, and 10.1 mL/100 mL, respectively.

**Pharmacokinetic studies**

Blood sampling is done at zero (predose), 0.5 hours, 1, 2, 3, 4, 5, 6, and 8 hours after the first dose. Subjects eat lunch and dinner after the 4-hour time point while in the ATU. On day 28, a full profile was done at zero (predose), 0.5 hour, 1, 2, 3, 4, 5, 6, 8, and 24 hours in the same manner. Blood samples were collected into a tube containing EDTA as the anticoagulant, centrifuged at 3,000 g within 30 to 60 minutes to produce plasma, frozen and maintained in a freezer at −20°C. Plasma concentration of pazopanib was determined using a validated analytical method based on protein precipitation followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for pazopanib was 100 ng/mL, using a 20 ul aliquot of human plasma with a higher limit of quantification (HLQ) of 50,000 ng/mL. The computer systems that were used on this study to acquire and quantify data included Analyst Versions 1.4.1 and 1.4.2, SMS2000 Versions 2.0, 2.1, and 2.2. Quality control (QC) samples, prepared at 3 different analyte concentrations and stored with study samples were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the...
nominal concentration by more than 15%, and at least 50% of the results from each QC concentration should be within 15% of nominal. The applicable analysis met all the predefined run acceptance criteria. All data are stored in the GLP Archive, GlaxoSmithKline Pharmaceuticals, Research and Development, Upper Merion.

**Statistical considerations**

This study followed a 2-stage phase II design with a primary endpoint of clinical benefit rate (CBR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, that is, complete response (CR), partial response (PR), or stable disease (SD). All patients on the study who had a documented SD, PR, or CR had a confirmation scan within 6 weeks of first response scan. This endpoint of CBR at 12 weeks was chosen as the investigators were concerned that pazopanib would exhibit a cytostatic and not cytotoxic effect on the tumor leading to disease stabilization rather than tumor reduction. We expected that pazopanib for advanced nasopharyngeal carcinoma was considered worthy of further study if the true CBR is at least 35%. On the other hand, a true CBR of no greater than 15% would discourage the justification of further testing of the proposed agent.

Using Simon’s optimal 2-stage design (30) with a type I error of 10% and power of 90%, a total of 33 patients is required. Nineteen patients were accrued for the first stage and if 3 or fewer responses are found, the trial will stop and the regimen would be declared not promising. However, if at least 4 responses were found, the trial would continue to recruit an additional 14 patients for stage 2. The cytostatic agent was considered worthy of a further testing if 8 or more responses out of 33 were reported. There was a 68% probability that the trial will terminate at stage one if the true response rate is less than 15%.

The analysis was done on an intention-to-treat basis. The CBR at 12 weeks was reported and its associated 95% CI was calculated using the formula described by Newcombe and Altman. The OS was calculated from the date of enrolment into the study to date of death from any cause or to the date when the patient was last known to be alive. The PFS was defined as the time of enrolment into the study to date of documented disease progression, or to the date when the patient was last known to be alive. Kaplan–Meier survival curves were obtained and used to estimate the median survival time. Toxicity profile was also assessed. The frequencies of grade 3/4 of each toxicity item were tabulated by treatment phase and follow up phase.

Pazopanib pharmacokinetic parameters were estimated on day 1 and day 28 and paired data for patients was analyzed by related samples Wilcoxon signed rank test to see the difference in PK parameters level within same set of subjects at different conditions, baseline, and steady state. Spearman’s ρ test was applied for pharmacokinetic-pharmacodynamic correlative studies. The level of significance, α, was kept 0.05 unless otherwise stated. All analyzes were done using SAS software (version 9.2; SAS, Inc.).

### Table 1. Patient demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 33)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>50 (36–68)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
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<tr>
<td>Chinese</td>
<td>31 (93.9)</td>
</tr>
<tr>
<td>Malay</td>
<td>2 (6.1)</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>23 (69.7)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (30.3)</td>
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<td>ECOG performance status</td>
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<td>0</td>
<td>10 (30.3)</td>
</tr>
<tr>
<td>1</td>
<td>23 (69.7)</td>
</tr>
<tr>
<td>Histopathologic type</td>
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<tr>
<td>Nonkeratinising carcinoma</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Undifferentiated or poorly differentiated carcinoma</td>
<td>31 (93.9)</td>
</tr>
<tr>
<td>Regimens of prior chemotherapy received</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1–7)</td>
</tr>
</tbody>
</table>

Values expressed as n (%), unless otherwise specified.

### Results

#### Patient characteristics

Thirty-three patients were accrued onto the trial between August 2007 and August 2009. All patients were ECOG 0-1 with median age of 50 years (range 36–68). This patient cohort was heavily pretreated and had received a median of 3 (range 1–7) prior chemotherapeutic regimens (Table 1).

#### Treatment responses

Tumor measurements were carried out every 6 weeks. There were no complete responses, 2 patients (6.1%) had confirmed partial responses, 16 (48.5%) had confirmed stable disease, and 11 (33.3%) had progressive disease. Four patients were not evaluable for disease status (2 died prior to evaluation, and 2 declined further evaluation, one of whom had an unconfirmed PR), giving a clinical benefit rate of 54.5% (95% CI: 38.0–70.2) at 12 weeks. Ten patients (30.3%) received more than 6 cycles (4 months) of treatment, and 7 (21.2%) had PR/SD that lasted at least 6 months (Table 2). The waterfall plot for response showed a reduction in tumor size in 60% of subjects at first response assessment (Fig. 1A). Central cavitation suggestive of tumor necrosis was observed in some patients, who otherwise had SD by RECIST criteria on confirmation scans (Fig. 1B).

#### Toxicities

One patient each died from epistaxis and myocardial infarction before response evaluation. The grade 3/4 toxicities encountered included fatigue (12.1%), hand-foot
syndrome (15.2%), anorexia (9.1%), diarrhea (6.1%), vomiting (6.1%), dehydration (3%), hypertension (3%), hyponatremia (3%), neutropenic fever (3%), proteinuria (3%), and pericardial effusion (3%). The complete toxicities experienced are described in Table 3.

Fourteen patients required dose reductions from 800 to 600 mg, and 6 patients required another further dose reduction to 400 mg. The dose reductions were related to fatigue (n = 5), hand-foot syndrome (n = 3), hypertension (n = 1), proteinuria (n = 1), vomiting (n = 1), transaminitis (n = 1), and pericardial effusion (n = 1).

Survival analysis
Two patients passed away without documented PD and are considered to have progressive disease at death in the analysis. The median time to tumor progression is 4.4 months (95% CI: 3.9–5.8 months). The median OS is 10.8 months (95% CI: 8.6–21.8 months). The OS of the patients at 1 year is 44.4% and the PFS at 1 year is 13% (Fig. 2).

Pharmacokinetic/pharmacodynamic correlative studies
Pazopanib pharmacokinetic parameters were estimated on D1 and D28 (steady state). Of the 33 patients recruited for the study, 26 patients had complete pharmacokinetic parameters estimated on D1 and D28 and were included in the final pharmacokinetic analysis for comparison of variations in pharmacokinetic values between D1 and D28. Seven patients were excluded from the final pharmacokinetic analysis due to missing sampling time points in 3 patients on D28 and inability to estimate pharmacokinetic parameters in 2 patients each on D1 and D28, respectively. The interpatient variability in pharmacokinetic parameters was very wide on D1 (AUIC0–24h/dose: 11.3-fold; Vd/F: 9.5-fold and CL/F/dose: 14.6-fold) and D28 (AUIC0–24h/dose: 52.4-fold; Vd/F: 96.5-fold and CL/F/dose: 30.2-fold). A significant increase in the AUIC0–24h/dose (approximately 1.4-fold; P < 0.001; Fig. 3A) and Vd/F (approximately 4.4-fold; P < 0.001) coupled with a slight decrease in CL/F (P = 0.08; Fig. 3B) were observed at steady state. The trough concentration of pazopanib on D28 was observed to be

Table 2. Tumor response to pazopanib

<table>
<thead>
<tr>
<th>Confirmed response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Stable</td>
<td>16 (48.5)</td>
</tr>
<tr>
<td>Progression</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Clinical benefit rate (95% CI)</td>
<td>54.5% (38.0–70.2%)</td>
</tr>
</tbody>
</table>

*Clinical benefit rate defined as complete and partial response and stable disease at 12 weeks.

Table 3. Toxicity possibly related to pazopanib (grade 3 or 4)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Pain: back</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (6.1)</td>
</tr>
</tbody>
</table>

Figure 1. A, waterfall plot showing best tumor response after pazopanib monotherapy in Nasopharyngeal carcinoma. B, cavitation of a lung metastasis after pazopanib therapy at 6 months compared with baseline.
above 15 μg/mL in approximately 92% of patients at steady state.

Nineteen of 33 patients had evaluable DCE-CT data. Four patients did not undergo DCE-CT imaging, 3 patients did not have posttreatment scans because of early disease progression, 7 patients had dynamic imaging data that failed to fit the DP tracer kinetic model because of motion misregistration, leaving 19 patients with evaluable DCE-CT data.

The mean baseline values of F, PS, v1, and v2 were 52.2 mL/100 mL/min, 18.6 mL/100 mL/min, 7.3 mL/100 mL, and 34.1 mL/100 mL, respectively. At steady state (D28), there were significant reductions in F, PS, and v1 from baseline to 35.7 mL/100 mL/min (mean reduction 31.7%, \( P = 0.005 \)), 10.1 mL/100 mL/min (45.7%, \( P < 0.001 \)), and 4.2 mL/100 mL (42.9%, \( P < 0.001 \)), respectively (Fig. 4A–D). All changes were greater than the 95% limits of change.

Pharmacokinetic-pharmacodynamic correlative studies showed a significant linear correlation between pazopanib AUC0–24 and the reduction in v2 at steady state (\( r = 0.54; P = 0.021 \)). A trend toward statistical significance was observed between pazopanib AUC0–24 and the reduction in PS at steady state (\( r = 0.45; P = 0.063 \)).

Patients who had progressive disease at 12 weeks were more likely to have a greater reduction in PS, compared with those who had stable or responding disease (76.6% vs. 31.6%; \( P = 0.034 \)). However, this was not significant on univariate regression (\( r^2 = 0.18; P = 0.09 \)). ROC analysis showed significant area under the ROC curve of 0.80 (\( P = 0.034 \)) for PS measurements between patients who had progressive disease, and those who had stable or responding disease. At day 28, a reduction in PS of greater than 68.2% from baseline had a sensitivity of 63% (95% CI: 24–91) and specificity of 100% (95% CI: 69–100) of predicting for progressive disease at 12 weeks. Using the optimal cutoff identified on ROC analysis, Kaplan–Meier survival curve was generated. Patients who had a reduction in PS of greater than 68.2% after pazopanib seem to have a poorer PFS. When compared with patients who had a reduction in PS of less than 68.2%, the HR for these patients is 7.12 (95% CI: 1.72–29.4). There were insufficient patient numbers to adjust for differences in patient characteristics between the 2 groups.

Discussion

Treatment for nasopharyngeal carcinoma remains an unmet need in the developing world. The burden of
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disease is large especially for countries whose populations derive their genetic pool from Southern China, and these countries include Singapore, Hong Kong, Taiwan, and the remaining countries in South-East Asia. Because of its inherent chemosensitive and radiosensitive biology, the spectrum of chemotherapeutics that could be used as salvage therapy is fairly wide. Together with limitations of drug access for drug development in Asia up until recently, this has hampered development of targeted therapeutics in nasopharyngeal carcinoma.

Early trials of small molecule inhibitors or monoclonal antibodies of epidermal growth factor receptor in nasopharyngeal carcinoma have met with poor results (31, 32). Pazopanib as an antiangiogenic agent in nasopharyngeal carcinoma represented a novel therapeutic modality. Although the drug does not seem promising by conventional RECIST criteria, there was clear activity as shown by tumor necrosis and cavitation reminiscent of that seen in GIST when treated with imatinib. Hence the disease stabilization rate is reasonable and the percentage of subjects that had durable disease stabilization of at least 6 months suggests that its use may be meaningful in nasopharyngeal carcinoma. The clinical benefit derived as above and the single fatal episode of epistaxis suggests its use in patients with bulky nasopharyngeal disease or patients who had previous reirradiation and osteoradionecrosis may need to be considered carefully. In a similarly designed monotherapy phase II study of sorafenib in a mixed population of squamous cell carcinoma of head neck (SCCHN) and nasopharyngeal carcinoma, only modest responses were described with also epistaxis in a nasopharyngeal location (33). However, what was striking in that study was a trend to a difference in the time to progression and OS seen between the SCCHN and nasopharyngeal carcinoma populations (1.8 vs. 3.2 months and 3.2 vs. 7.7 months). Although it is not adequate to compare across trials, the durations of PFS and OS seen in this study are comparable. The role of pazopanib and possibly even other antiangiogenic agents in the paradigm of nasopharyngeal carcinoma treatment could hence be envisaged as maintenance therapy in patients where there is minimal residual disease after primary cytoreduction in the first-line metastatic setting with chemotherapy.

DCE-CT has been established as a valid and reproducible clinical tool to monitor tumor vascular changes following treatment with antivascular therapies in early clinical trials. The DP tracer kinetic model offers the possibility of providing distinct measurements of blood flow and permeability. Such information would be of significance in clinical trials of antiangiogenic drugs, potentially allowing measurements of increased tumor blood flow and reduced permeability, reflecting vascular normalization. Furthermore, a model that can more accurately describe actual tumor biological changes following therapy may be a better predictor of drug exposure and clinical outcome. Seven of 26 patients had dynamic CT data that failed to fit the DP tracer kinetic mode because of image misregistration from voluntary patient movement. This was consistent with previous DCE-CT studies in lung tumors, where 6 of 16 dynamic studies could not be analyzed because of respiratory motion (34).

Nevertheless, the DCE imaging in this study suggests that the mode of activity of the drug is by antiangiogenesis. Significant reductions in F, PS, and v1 were observed after treatment with pazopanib, consistent with its antiangiogenic mode of action. The nonsignificant correlation between increasing pazopanib AUC(0–24) and reduction in PS, is suggestive of a dose effect. Unexpectedly, we observed that patients, who had greater reductions in PS, were more likely to have progressive disease. ROC analysis was able to identify a threshold in the change in PS, at which patients were more likely to have progressive disease after treatment with pazopanib. Furthermore, patients who achieved a reduction in PS of greater than 68.2% had a shorter PFS (HR 7.12; 95% CI: 1.72–29.4). The precise mechanism of reduction in PS remains unclear, and may be attributed to the degree of inhibition of the VEGF signaling axis with different drug concentrations, and direct effects on pericytes via PDGFR-β, both of which have crucial roles in endothelial cell organization and vessel integrity (35, 36).

The fact that greater reductions in permeability was associated with worse patient outcomes, raises the possibility that excessive inhibition of the VEGF signaling axis may be detrimental, perhaps as a result of hypoxia-related compensatory mechanisms (37). This is supported by preclinical data showing that antiangiogenic TKIs, for example, sunitinib, can conversely lead to enhanced invasion and promote metastases in relevant mouse models (38, 39). Interestingly, these effects were largely schedule and dose dependent, and it has been suggested that rational combinations of drugs may be able to abrogate such undesirable effects.

The extracellular-extravascular volume is represented by v2. Measurements of v2 are influenced by blood flow, permeability, vascular oncotic pressure, interstitial fluid pressure, and tumor cellular volume and can be considered a composite imaging biomarker, which might explain why there was no significant overall change 28 days following treatment with pazopanib. Following antiangiogenic therapy, the decrease in blood volume, reduction in vascular surface area, and drop in interstitial fluid pressure is balanced against the effects of improved extravasation of contrast from normalized vasculature. However, changes in v2 following treatment with pazopanib correlated significantly with drug exposure as measured using AUC(0–24), suggesting a dose effect. The reason for this is unclear and warrants further study into the role of v2 as a biomarker of tumor vascular response.

A necessary limitation of functional imaging to measure tumor blood flow is the decrease in organ coverage as a result of the need for a high temporal resolution. This may mean that the entire tumor volume may not be evaluated.
and thus the influence of tumor spatial heterogeneity may not be fully assessed.

The pharmacokinetics of a daily dose of 800 mg once a day in this all Asian population shows that AUC_{0-24} is higher at day 28 than day 1, and the t_{1/2} and MRT_{0-inf} is longer at day 28 than day 1. In addition, these levels were at least 20% higher than reported levels in a Western population (40) at steady state and could have resulted in the some of the toxicities encountered and the dose reductions needed due to excessive fatigue and hand-foot syndrome. Approximately 15% of patients experienced toxicity due to hand-foot syndrome as opposed to none in the study by Hurwitz and colleagues (40) possibly reflecting interethnic differences in sensitivity to pazopanib. There was one subject with hypothyroidism that developed as a result of pazopanib treatment of less than 6 months. Of interest is also the development of generalized hypopigmentation in subjects who had been on prolonged therapy. We consider this to be an effect of therapy rather than a marker for response and may be a reflection of c-kit inhibition as this loss of pigmentation has also been described in other drugs that target c-kit (41). The rates and grades of hypertension and proteinuria encountered on this study were low despite the higher drug exposure levels hence regular blood pressure monitoring and urine dipstick testing may not be necessary in Asian populations. The variable toxicity and pharmacokinetic profile observed in this cohort of Asian patients with nasopharyngeal carcinoma, suggest that additional studies may be needed to better define the dose of pazopanib in Asian patients.

In summary, pazopanib was found to be an active agent in nasopharyngeal carcinoma. The role of functional imaging as a predictive biomarker is encouraging and will need to be further validated. Confirmatory studies into the clinical efficacy and safety in a larger group of patients with a better defined dose schedule needs to be done. Further studies incorporating pazopanib with active cytotoxic combinations can be explored. However, the added toxicities of pazopanib to cytotoxics may limit the ability of patients to tolerate concurrent administration. Perhaps a sequential schedule of cytotoxics to effect tumor reduction followed by maintenance pazopanib is feasible and may be beneficial in prolonging tumor control. Further studies into targeted therapeutics for nasopharyngeal carcinoma should continue.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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