Evaluating the efficacy of pazopanib prior to planned nephrectomy in metastatic clear cell renal cancer: A phase II clinical trial

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Abstract

Importance: The role of cytoreductive nephrectomy in patients with metastatic renal cancer in the era of targeted therapy is uncertain. Data on targeted therapy prior to nephrectomy is lacking.

Objective: To establish the safety and efficacy of upfront pazopanib prior to cytoreductive nephrectomy in previously untreated metastatic clear cell renal cancer.

Design: A single-arm phase II study which recruited 104 patients between June 2008 and October 2012. The minimum follow up for patients was 30 months.

Setting: Cancer treatment centres with access to nephrectomy services.

Participants: Previously untreated patients with metastatic clear cell renal cancer.

Intervention: 12-14 weeks of pre-operative pazopanib prior to planned cytoreductive nephrectomy. Patients continued on pazopanib after surgery. Treatment was stopped at disease progression.

Main outcome measures: The primary endpoint was clinical benefit (SD, PR, CR using RECIST v1.1) prior to surgery (at 12-14 weeks). The secondary endpoints included surgical complications, progression free survival (PFS), overall survival (OS) and biomarker analysis.

Results: 104 patients were recruited, (94% with MSKCC intermediate or poor risk disease). Overall, 84/100 (84% [95% CI: 75% - 91%]) gained clinical benefit, before planned nephrectomy. The median reduction in the size of the primary tumor was 14% (inter-quartile range: 1% – 21%). No patients became inoperable due to local progression of disease. Nephrectomy was performed in 63 (61%) of patients: 14 (22%) reported surgical complications. The two commonest reasons for not having surgery were progression of disease (n=13) and patient choice (n=9). There was 1 post-operative surgical death. The median PFS and OS for the whole cohort were 7.1 months (95% CI: 6.0 – 9.2) and 22.7 months (95% CI: 14.3 –N.E) respectively. Patients with MSKCC poor risk disease or progressive disease

prior to surgery had a poor outcome. Biomarker analysis from sequential tissue revealed significant reduction in expression of VHL, HIF, MET and increased PD-L1 expression in the immune component. No on treatment biomarker correlated with response.

Conclusions and relevance: Nephrectomy after upfront pazopanib can be performed safely and is associated with good outcomes in patients with intermediate risk disease. This approach is a treatment consideration for this group of patients.

Trial Registration: NCT01512186

Introduction

The role of cytoreductive nephrectomy for advanced clear cell renal cancer patients (ccRCC) who present with a synchronous renal mass and metastasis is uncertain. The current standard of care is cytoreductive nephrectomy followed by vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI)[1]. The use of nephrectomy in metastatic disease was established prior to the development of VEGF TKIs[2,3]. This sequence has not been prospectively evaluated in the era of VEGF targeted therapy, although large recent retrospective series suggest nephrectomy is still associated with a survival benefit in unselected patients[4]. A potential problem with this sequence is that there is a significant delay in starting VEGF targeted therapy while patients are recovering from the nephrectomy. This is of particular concern for patients with aggressive disease or poor prognostic features where any delay in disease control may be detrimental[4-6].

An alternative approach is to give upfront systemic therapy prior to the nephrectomy. This has theoretical advantages in that systemic therapy can commence more rapidly, and there may be significant shrinkage of the primary tumor facilitating surgery. It is also possible that this upfront approach selects out patients with rapidly progressive VEGF resistant disease who have a very short life expectancy and may not benefit from nephrectomy[5,7]. There are also potential risks to this approach. Nephrectomy may enhance the systemic response to VEGF therapy by reducing the tumor burden. Also, significant time off systemic therapy is required during the peri-operative period which may allow for the development of resistance to therapy. Finally it has been reported in previous small safety studies that although this upfront approach is feasible, surgery may be more complex due to additional treatment related necrosis and delayed wound healing[7,8].

Therefore in this study we planned to prospectively evaluate the efficacy of this upfront approach by giving up to fourteen weeks of pazopanib prior to nephrectomy.

Biomarker analysis from tissue taken prior to therapy has not resulted in predictive markers in ccRCC[9]. We hypothesised that tissue taken before and during therapy may facilitate biomarker discovery. Due to the nature of the design of this study, sequential tissue was available from pre-treatment samples and at the time of surgery, allowing for assessment of biomarker evaluation on treatment.

Methods

Patient population

The study population included treatment-naive patients with histologically confirmed metastatic ccRCC. Patients were required to be fit for both pazopanib and nephrectomy, have adequate end organ function, be able to give informed consent and have an ECOG performance status of 0 or 1. Patients with a prior nephrectomy for renal cancer were excluded. Other exclusion criteria focused on contraindication for pazopanib such as uncontrolled bleeding, hypertension or cardiovascular disease.

This was a multi-centre single arm trial enrolling from 12 centres across the United Kingdom. The study has appropriate ethical and regulatory approval (NCT01512186). All patients participated with written informed consent.

Study design and sample size

Patients were planned to receive 12-14 weeks of pazopanib (800 mg daily) prior to cytoreductive nephrectomy (open or laparoscopic), which took place at least 48 hours after the last dose of systemic treatment. A 14-day treatment break was required after surgery. Pazopanib therapy was then continued every 6 weeks, until disease progression was recorded. Patients who exhibited disease progression during the treatment break were allowed to continue pazopanib if it was deemed to be of clinical benefit. Dose reductions of pazopanib

followed standard guidelines. Surgery could be brought forward based on clinical grounds after discussion with the medical monitor. Treatment delays of up to 28 days were permitted. The primary endpoint of the trial was to achieve a clinical benefit rate of above 75% at the time of the pre-surgical tumor assessment. Clinical benefit was defined as patients who did not have clinical or radiological progression of disease (RECIST v1.1). The numbers of fully evaluable patients (95) were generated using Simon 2 stage optimal design. It had a 90% chance of concluding that pazopanib is active if the true clinical benefit rate was 75% or more but only a 5% chance of concluding it was active if the clinical benefit was less than 60%. An interim analysis occurred after recruitment of the first 34 patients, 22 of which were required stabilization to proceed to the 2nd stage. As the primary endpoint was clinical benefit at 12-14 weeks it was planned to recruit approximately 125 patients to account for patients who drop out during this period.

Secondary endpoints included progression free survival (PFS) by RECIST v1.1, overall survival (OS), the frequency of adverse events by CTCAE v4.0 and the evaluation of surgical complications by Clavien Dindo classifcation. Disease assessment was performed at baseline, 6 weeks into systemic treatment, pre-nephrectomy (12-14 weeks after the start of pazopanib), 6 weeks post nephrectomy and then at 12 weekly intervals. Radiology review occurred according to investigator assessment.

Statistical analysis

The primary endpoint was calculated as clinical benefit rate, with 95% confidence interval. PFS and OS were assessed using the Kaplan Meier method. The 31st of July 2014 was used as a censoring date for patients who had not progressed or died. In survival analysis, prognostic value of the baseline factors were assessed via Cox proportional hazards regression model. The assumption of proportional hazards was tested by examining plots of complementary

log-log (event time) versus log(time). Intercooled STATA 13.0 (STATA Corp, College Station, TX, USA) was used for the statistical analysis.

Biomarker analysis.

A tissue microrarray (TMA) was constructed from biopsy and nephrectomy tissue samples. The following antibodies were used to assess biomarker expression, PDL-1 (Abcam), c-met (Life Technologies), HIF-1a (Novus Biologicals), VEGFR2 (Cell Signalling) and VHL (BD Pharmingen). Expression in untreated and treated samples was compared using validated immunohistochemistry protocols for each antibody. A single pathologist scored the immunohistochemical expression. The immunohistochemical scoring was performed independently and blinded to patient outcome data for each antibody.

Multiple samples were taken in the nephrectomy samples (n=5) where possible to allow for intratumoural heterogeneity (median scores were taken). Two-sample t-test was used to test the difference of biomarker values between treated and untreated patients. Prognostic significance of biomarkers were assessed via Cox proportional hazards regression model.

Results

Patient characteristics at diagnosis and at surgery

104 patients were recruited and received study drug. Patent's baseline demographics are shown in eTable 1. Seventy eight patients (76.5%) were male. The median age was 64 years (inter-quartile range: 56 – 71). Liver or bone metastasis were present in 44 patients (42%), while 63 patients (61%) had T3-4 tumours. The median size of the primary tumour was 10cm (IQR: 8.3-11.6cm). 82% and 18% had MSKCC intermediate and poor risk disease respectively.

Efficacy of upfront pazopanib.

Of the 104 patients recruited, 100 patients were assessable for clinical benefit prior to planned nephrectomy (consort diagram Figure 1). 4 were not assessable as they came off drug for toxicity prior to radiological assessment for clinical benefit. The primary objective of the trial was achieved with 84/100 [84% (95% CI: 75% - 91%)] patients achieving clinical benefit. 13 (13%) of patients had a partial response to therapy, 16 (16%) had progression of disease, the remainder, had stable disease 71 (71%).

The median duration of therapy prior to surgery was 13 weeks (range 11-14). The median size of the primary tumour before and after pazopanib was 10.0cm (IQR 8.3 –11.6) and 8.3cm (IQR 6.8 – 10.9) respectively. Median reduction of the primary tumour was 14.4% (IQR: 1.4-21.1, Figure 2). The median PFS and OS for the 104 patients enrolled was 7.1 months (95% CI: 5.98 – 9.23) and 22.7 months (95% CI: 14.3-NE) respectively (Figure 2b). Patients who failed to achieve clinical benefit have shorter overall survival compared to those with clinical benefit (median overall survival 3.9 months (95% CI: 0.5 – 9.1) vs. 24.0 months (95% CI: 18.4 - NE), HR (95%CI): 3.92 (1.78 – 8.63), eFigure 1). Eighteen (18%) patients had MSKCC poor risk disease, 7 (39%) of these patients had PD as the pre-surgery response and only 8 (44%) had surgery. These MSKCC poor risk patients had a median PFS and OS of 3.9 months (95% CI: 1.7 – 7.5) and 5.7 months (95% CI: 2.6 – 10.8) respectively (eFigure 2). Progression of disease during the 6 week treatment interval occurred in 25% of the patients who had nephrectomy.

Univariable survival analysis for age, gender, MSKCC score, tumor T stage, presence of bone, brain liver metastasis and performance status at baseline identified only MSKCC score as a significant prognostic marker for PFS (HR 2.46 (95% CI 1.44-4.21).

Evaluation of surgical safety

Of the 104 patients, 65 (63%) had nephrectomy. The 3 commonest reasons for not having nephrectomy were progression of systemic disease n=13, patient choice n=9 and the patient being surgically unfit n=5.

Open nephrectomy occurred in 68%, the remainder had a laparoscopic nephrectomy. The median post operative hospital stay was 7 days (IQR: 5-8). Median surgical time was 3 hours (IQR 1.8-3.9). There was one surgery related death. Surgical complications were observed in 14 (22%) of the nephrectomies, including bleeding (8%) delayed wound healing (6%) splenectomy (3%) and raised creatinine (2%) (eTable 2). Of the surgical complications, 2 (3%) were grade 3-4 (Clavien Dindo). The median blood loss was 450 ml (IQR 100 – 725), surgical time 3 hours (IQR 1.8 – 3.9) and median hospital stay 7 days (IQR 5 – 8) (eTable 2). 90% of the operations revealed a T2-4 tumor underlining the advanced stage of disease of these patients.

Toxicity profile

Adverse events were in line with those previously reported with pazopanib[10]. Grade 3 /4 adverse events occurred in 28% of patients. The commonest toxicity (any grade) was fatigue (88%), diarrhoea (53%), hypertension (50%) and hand and foot syndrome (32%) (eTable 3). Pazopanib dose was reduced in 26 patients (25%) pre-surgery. 4 patients discontinued therapy for AEs.

Biomarker analysis

There was a significant decrease of expression of VEGFR2, HIF1 alpha, c-met and VHL after pazopanib ($p<0.05$ for each) (figure 3 and eFigure 3). PD-L1 expression in the immune component increased with therapy ($p<0.05$), while CD8 expression reduced ($p=0.05$). Further on treatment biomarker analysis showed none of the biomarkers correlated with survival outcome or response (figure 3c and 3d, eTable 4, eFigure 4). Intratumoral biomarker

variability was evident for PD-L1 expression on multiple testing with only 46% of patients consistently scoring the same when 5 samples from the same tumor were analysed.

Discussion

There is a lack of prospective data for ccRCC patients who present with a synchronous renal tumour and metastatic disease in the era of targeted therapy. These patients have a poor outcome, which is supported by retrospective series and prognostic scoring systems[4,5]. There is also uncertainty about the role and timing of nephrectomy. In this study, 12-14 weeks of pazopanib was given prior to nephrectomy. The aim was to induce stability of disease prior to nephrectomy in over 75% of patients, avoiding potential progression and clinical deterioration during the preoperative surgical period. The PFS and OS results [7.1 months and 22.7 months respectively] were acceptable and in line with those seen for similar risk groups in the pivotal randomized VEGF targeted therapy trials in which the majority of patients previously had nephrectomy[10-12]. Survival analysis showed that the prognostic factors in this specific group of patients are similar to those in unselected patients. MSKCC prognostic score was significant.

This approached appeared safe with low surgical morbidity, acceptable levels of surgical complications and very low surgical related mortality (2%). However, there were areas of concern. Delays in wound healing, thought to be related to VEGF targeted therapy, were reported in this and other smaller series[7]. Also, 39% of patients did not have nephrectomy. This is higher than figures for nephrectomy prior to systemic therapy and is probably due to patients with primary progressive disease not have nephrectomy[2]. It appears sensible not to perform nephrectomy on these patients with primary progressive metastatic disease, as it spares them a procedure which causes morbidity but may not significantly improve outcome. It also allows them to switch to potentially more effective systemic therapies[13,14]. Patients

with progression of disease at 14 week (the time of assessment) had a poor outcome justifying this approach (eFigure 1). A 2nd smaller group did not have nephrectomy because of the development of morbidity. Pazopanib is associated with a spectrum of side effects, which may have contributed to this[10]. This group of patients is a concern as nephrectomy prior to pazopanib may have been possible and may have improved outcome. Finally, a group chose not to have nephrectomy. This was in part due to patients who were responding well to therapy and were reluctant to stop therapy for surgery. This group of patients is small but had a good outcome (data not shown). In an era where there is uncertainty regarding the benefits of cytoreductive nephrectomy, this appears to be a pragmatic approach and not necessarily of concern.

Another group of patients, requiring particular attention, are those with MSKCC poor risk disease at baseline. These patients had a poor outcome irrespective of whether they had surgery (median overall survival <6 months, eFigure 2). Previous retrospective analysis of other smaller prospective series with sunitinib suggested that nephrectomy was not recommended in this setting[4,15]. Our data supports this recommendation with the most robust data to date. These issues will be further addressed within 2 randomized trials testing the role and timing of nephrectomy in metastatic ccRCC (NCT00930033, NCT01099423). Comparisons with pazopanib and sunitinib are not possible in this setting, largely due to the small size of the studies and variability in protocol design[7]. Both drugs have clinical benefit rates above 70% in this setting although the sunitinib trials focused mainly on safety rather than efficacy. Previous non-inferiority studies show these agents are non-inferior in terms of efficacy with differing adverse event profiles[11]. Our results support these findings. The data presented here are to our knowledge the most robust and pazopanib appears well tolerated and efficacious.

To date pretreatment predictive biomarkers have not been identified for VEGF targeted therapy[9]. We hypothesized that biomarker analysis after a period of therapy could identify subgroups of patients who benefit from VEGF therapy. It was possible to test this hypothesis in our trial due to the nature of the design and the relatively large numbers compared to previous studies[16]. Results showed significant decreases in VEGF related biomarkers (HIF, VEGFR2 and VHL) with therapy. However, suppression of VEGF related biomarkers did not correlate with outcome. It may be that the timing of the analysis was too early as the majority of patients were still benefiting from therapy. A third sample at progression would have potentially helped address this issue. We explored the effect of pazopanib on PD-L1 and MET expression, both of which are active targets in ccRCC after VEGF targeted therapy[13,14]. Results showed significant decreases to VEGF related proteins such as VEGFR2 as expected[16]. However pazopanib was also associated with an increased PD-L1 expression in the immune component in conjunction with a fall in CD8 count. Both PD-L1 and CD8 expression are of prognostic significance in renal cancer[17]. These results underline the potential immunogenic effects of VEGF TKIs and the problems associated with archived untreated tissue for PD-L1 biomarker analysis in VEGF resistant ccRCC[14].

Intratumor heterogeneity of PD-L1 expression seen in our treated samples further complicates these issues. Cabozantinib is a MET (and VEGF) inhibitor with activity in VEGF resistant metastatic ccRCC[13]. Pazopanib reduced MET expression, again questioning the value of historical tissue for biomarker expression. Although significant changes occurred to a spectrum of proteins, none correlated with response, suggesting on treatment biomarker expression may not be a breakthrough in biomarker discovery in this setting as originally hoped.

This work has shortcomings, notably the trial was not randomized and the duration of therapy prior to the nephrectomy was fixed. Also the biomarker analysis was limited due to many of

the patients with progressive disease not having surgery and the challenges around processing nephrectomy biopsy tissue. Finally, some of the detail regarding the surgery, such as thrombectomy and use of anticoagulation therapy was not collected. Nevertheless this clinical approach is potentially attractive to subsets patients, particularly those who are keen to start therapy quickly, and those who do not have MSKCC poor risk disease.

Upfront targeted therapy does not adequately reduce the size of the primary tumor to recommend this approach to facilitate surgery. However the approach achieves rapid control of disease in the majority of patients and is associated acceptable outcomes. Pazopanib appears an attractive agent in this setting due to its positive adverse event profile[11]. Our results question the role of CN in MSKCC poor risk disease in a single prospective study for the first time.

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All information and materials in the manuscript are original.

Author Contributions

Professor Thomas Powles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Powles

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Powles, Sarker

Critical revision of the manuscript for important intellectual content: All authors.

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Author Conflict of Interests

The following authors have Conflict of Interests to declare:

- Powles T – Honoraria (Roche/Genentech, Bristol-Myers Squibb, Novartis), Consulting or Advisory Role (Roche/Genentech, Bristol-Myers Squibb, Merck), Research Funding (AstraZeneca/MedImmune, Roche/Genentech, GlaxoSmithKline)
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Figure 1: Consolidated standards of reporting trials (CONSORT) flow diagram

Figure 2: (a)Percentage change of primary renal carcinoma following therapy with pazopanib (median reduction = 14.4% (IQR: 1.4-21.1) (n=95). (b) Kaplan Meier curve showing progression free survival for the intention to treat population (n=103)

Figure 3: Molecular markers before and after pazopanib therapy. There was a significant decrease of expression of VEGFR2 (fig. 3a) and increase of PD-L1 (fig 3b) in the immune component. Change also occurred with C-MET (n=59), CD8 (n=62) and VHL (n=57) after pazopanib ($p<0.05$ for each) which are shown in supplementary data (eFigure 3). 3b None of these biomarkers correlated with response in the primary tumor which is shown in figure 3c and 3d (waterfall plot comparing VEGFR2 and PD-L1 immune component expression on therapy and response) and supplementary data.