A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma

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Purpose: Preservation of renal function is prioritized during surgical management of localized renal cell carcinoma. VEGF targeted agents can downsize tumors in metastatic renal cell carcinoma and may do the same in localized renal cell carcinoma, allowing for optimal preservation of renal parenchyma associated with partial nephrectomy.

Materials and Methods: Localized clear cell renal cell carcinoma patients meeting 1 or both of the following criteria were enrolled in a prospective phase II trial, including radical or partial nephrectomy likely to yield a glomerular filtration rate of less than 30 ml/minute/1.73 m^2, or partial nephrectomy high risk due to high complexity (R.E.N.A.L. 10 to 12) or tumor adjacent to hilar vessels. Pazopanib (800 mg once daily) was administered for 8 to 16 weeks with repeat imaging at completion of therapy, followed by surgery.

Results: A total of 25 patients enrolled with a median tumor size of 7.3 cm and a median R.E.N.A.L. score of 11. Of index lesions 80% were high complexity and 56% of patients had a solitary kidney. Patients received a median of 8 weeks of pazopanib. The median interval from treatment start to surgery was 10.6 weeks. R.E.N.A.L. score decreased in 71% of tumors and 92% of patients experienced a reduction in tumor volume. Six of 13 patients for whom partial nephrectomy was not possible at baseline were able to undergo partial nephrectomy after treatment. The mean parenchymal volume that could be saved with surgery increased from an estimated 107 to 173 cc ($p = 0.0015$). In 5 patients a urine leak developed, which was managed conservatively, and 7 received a transfusion, of whom 1 required embolization.

Abbreviations and Acronyms

AE = adverse event
CKD = chronic kidney disease
CT = computerized tomography
eGFR = estimated GFR
GFR = glomerular filtration rate
PN = partial nephrectomy
RCC = renal cell carcinoma
R.E.N.A.L. = R (radius), E (exophytic/endophytic properties), N (nearness to collecting system or sinus), A (anterior/posterior), L (location relative to polar lines)
RN = radical nephrectomy
VEGF = vascular endothelial growth factor

Accepted for publication March 3, 2015.
Study received Case Comprehensive Cancer Center and Fox Chase Cancer Center institutional review board approval.
* Financial interest and/or other relationship with GlaxoSmithKline and Cleveland Clinic Foundation.
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0022-5347/15/1942-0297/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.03.096
Vol. 194, 297-303, August 2015
Printed in U.S.A.

Conclusions: Neoadjuvant pazopanib resulted in downsizing localized renal cell carcinoma, allowing for improved preservation of renal parenchyma and enabling partial nephrectomy in a select subset of patients who would otherwise require radical nephrectomy.

Key Words: kidney; carcinoma, renal cell; nephrectomy; pazopanib; neoadjuvant therapy

Absolute indications for PN include patients for whom loss of nephrons would place them at risk for requiring renal replacement therapy, such as those with a solitary kidney or preexisting CKD.[1] PN in such settings should be optimized to preserve as much functioning parenchyma as possible.[1–3] However, many tumors may not be amenable to PN due to tumor size and/or location.

A variety of VEGF receptor inhibitors have demonstrated the ability to decrease tumor volumes in patients with advanced RCC.[4–8] The limited experience with these agents for locally advanced primary tumors has been encouraging as well, in contrast to data from the cytokine era, when primary tumor responses were rare.[9] A previous trial of sunitinib for locally advanced, unresectable RCC showed that 96% of clear cell tumors exhibited at least some shrinkage and the partial response rate was 33%.[10] Responses in nonclear cell tumors were not observed. Of patients with clear cell RCC 59% were able to proceed to surgery, most often RN. Other reports also substantiate the potential efficacy and safety of VEGF targeted agents in the neoadjuvant setting.[11–15] Based on these data, the potential role of pazopanib for downsizing primary clear cell RCC to enable or optimize PN in patients with priority for preservation of renal function was investigated. Surgical safety was evaluated as a secondary end point given the potential effects of VEGF targeted agents on tissue healing and thromboembolic events.[14,16,17]

METHODS

Study eligibility criteria included patients with localized, biopsy proven clear cell RCC with a need for optimal preservation of renal parenchyma based on 1) RN or PN would yield GFR less than 30 ml/minute/1.73 m^2 and/or 2) anticipated increased risk of morbidity with PN due to high complexity (R.E.N.A.L. score 10 to 12) or hilar tumor location. Additional eligibility criteria included ECOG (Eastern Cooperative Oncology Group) performance status 0 or 1 and adequate organ function. Study exclusion criteria were prior systemic therapy for RCC, evidence of metastatic disease, bleeding diathesis or coagulopathy (hematuria allowed), significant cardiovascular disease, prolonged QT interval or hypertension that could not be controlled medically. This study was approved by the institutional review boards of Case Comprehensive Cancer Center and Fox Chase Cancer Center, and all patients provided written informed consent.

Patients underwent CT of the chest/abdomen/pelvis at baseline and 8 weeks, and at completion of therapy. CT of the brain and bone scan were also performed at study entry and repeated only if suggestive signs/symptoms developed. Pazopanib was administered at 800 mg by mouth daily for up to 16 weeks. Toxicity was graded according to CTCAE (Common Terminology Criteria for Adverse Events), version 4.0. Patients with unacceptable toxicity had pazopanib held until resolution and then were dose modified per existing guidelines to 600 or 400 mg daily. If toxicity persisted after dose reduction to 400 mg, treatment was discontinued. After 8 weeks of therapy and again at completion patients were re-imaged and counseled for intervention at surgeon discretion. Pazopanib was held at least 7 days prior to surgery. Perioperative events were classified according to the Clavien-Dindo scheme.[18]

PN was performed using standard open or robotic approaches with or without hypothermia at surgeon discretion. Hilar clamping was performed in all cases. Surgical efforts focused on optimizing preservation of vascularized parenchyma during tumor excision and renal reconstruction, while still obtaining negative margins.

The primary end point was the percentage of patients who could undergo PN after pazopanib therapy. Trial design was based on the assumption that if the proportion of patients that have a reduction of tumor burden to permit PN is 15% or less, then pazopanib therapy has little or no effect for this purpose. Alternatively, if 40% or more of patients are able to proceed to PN, then pazopanib therapy would be considered effective. A total of 30 patients were to be enrolled, including 15 in the first stage and 15 in the second. If after treating the first 15 patients only 0 or 1 patient was able to undergo PN, the study would be stopped due to lack of activity. If 9 or more of the 30 patients were able to undergo PN, then the null hypothesis would be rejected. The type I error rate of this design was 0.05 and the power was 90%.

A secondary end point was the amount of vascularized parenchyma that could be saved with surgery after pazopanib therapy compared to pretherapy assessment. Measurement of the total parenchymal volume and the amount that could be saved by PN was performed using volumetric analysis of CT images as previously described.[19] The amount of parenchymal mass that could be saved by PN presumed loss of a 5 mm rim of normal parenchyma around the tumor that would be excised or devascularized with PN along with any radial parenchymal tissue that would also be devascularized.[19] Secondary end points also included reduction of tumor diameter and volume, and RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1[20]) defined objective response rates, safety and surgical morbidity.