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Phase II Trial Of Neoadjuvant Axitinib In Patients With Locally Advanced Non-Metastatic Clear Cell Renal Cell Carcinoma

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Abstract

Background—Previous studies have shown modest impact of tyrosine kinase inhibitors on primary renal tumors. These studies were mostly retrospective and heterogeneous in their eligibility criteria with regards to histology, disease stage, duration of therapy, and time off therapy prior to surgery.

Objective—To prospectively investigate the safety and efficacy of axitinib in downsizing tumors in patients with non-metastatic biopsy-proven clear cell renal cell carcinoma (ccRCC).

Design, Setting, and Participants—This is a single-institutional, single-arm phase 2 clinical trial. Patients with locally-advanced non-metastatic biopsy-proven ccRCC were eligible. This trial was registered with clinicaltrials.gov (NCT01263769).

Intervention—Patients received axitinib 5mg for up to 12 weeks. Axitinib was continued until 36 hours prior to surgery. Patient underwent partial or radical nephrectomy after axitinib therapy.

Outcome Measurements and Statistical Analysis—The primary outcome was objective response rate prior to surgery. Secondary outcomes included safety, tolerability, and quality of

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Clinical Trial Registration

This clinical trial was registered with clinicaltrials.gov (NCT01263769).

Christopher G. Wood had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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life. A dedicated radiologist independently reviewed all CT scans to evaluate for response using RECIST.

Results and Limitations—Twenty-four patients were treated. 22 patients continued axitinib for 12 weeks, while 1 patient continued axitinib for 11 weeks, and underwent surgery as planned. One patient stopped treatment at 7 weeks due to adverse events. Median reduction of primary renal tumor diameter was 28.3%. Eleven patients experienced a partial response by RECIST; 13 had stable disease. There was no progression of disease while on axitinib. The most common AEs were hypertension, fatigue, oral mucositis, hypothyroidism, and hand-foot syndrome. Postoperatively, 2 grade 3 and 13 grade 2 complications were noted. No grade 4 or 5 complications occurred. FCSI (Functional Assessment of Cancer Therapy-Kidney Specific Index-15) changed over time, with quality of life worsening while on therapy, but by week 19, it was not statistically different from screening. Limitations include single-arm design and small patient numbers.

Conclusions—Axitinib was clinically active and reasonably well tolerated in the neoadjuvant setting in patients with locally-advanced non-metastatic ccRCC.

Keywords

Neoadjuvant; renal cell carcinoma; targeted therapy; clinically localized; clinical trial

INTRODUCTION

Targeted therapy has broadened the horizon of treatment in patients with metastatic clear cell renal cell carcinoma (ccRCC), with its widespread use since 2006. Several agents targeting the VEGF and mTOR pathways important in the biology of clear cell renal cell carcinoma have been developed and utilized since then, with sequential refinements in the specificity of molecular targeting as well as improvements in tolerability and side effect profiles. The relative ease of administration of recently developed oral targeted therapies has led to their use in patients with their primary renal tumor in place, most commonly in poor surgical candidates and patients with unresectable primary renal tumors.

Around the time this current study was designed, one such molecule, axitinib—an oral tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3—was studied in 52 patients with metastatic ccRCC who failed prior systemic therapy with Interferon- α or Interleukin-2 (1). Responses were seen in 23 patients (44.2%), with two patients achieving complete response and one patient without prior nephrectomy having partial shrinkage of the primary renal tumor. Axitinib was also studied in 62 patients with metastatic ccRCC refractory to sorafenib (2), and a partial response was observed in 22.6% of patients, with 80% experiencing some degree of tumor shrinkage. As such, axitinib appeared to be a promising agent in the treatment of metastatic ccRCC. In 2010, given the promising data available then with axitinib, we decided to conduct a prospective trial in patients with non-metastatic RCC with the primary renal tumor in situ using this particular agent. Since then, based on results from a phase III clinical trial, axitinib had been approved for use in second-line setting in patients with metastatic ccRCC(3). Potential advantages of neoadjuvant therapy include downsizing and/or downstaging of tumors to change surgical approach from radical to

partial nephrectomy or from open to minimally-invasive surgery, and to allow for resection of unresectable tumors. Few registered prospective clinical trials were conducted and reported to date in this disease setting.

PATIENTS AND METHODS

Eligibility Criteria

This study was designed as a prospective, single-center, open-label, non-randomized phase II study of axitinib for 12 weeks prior to curative surgery in patients with locally advanced non-metastatic clear cell RCC.

Patients were eligible for this study if they had clinical stage T2-T3b (using AJCC 2010(4)) without any radiographic evidence of nodal or distant metastases, clear cell histology on pretreatment biopsy of the primary renal tumor, tumor amenable for curative surgery, ECOG performance status(5) of 0 or 1, adequate renal, liver, and bone marrow function, and did not have any other cancers in the 5 years preceding diagnosis of their renal cancer.

The study was approved by the Institutional Review Board and registered with [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01263769)(NCT01263769). Informed consent was obtained prior to study enrollment.

Drug treatment

Axitinib was administered orally at a starting dose of 5mg twice daily. Dose adjustments were based on adverse events experienced by the individual patient, and were determined by the treating physicians. Pill counts were used to document treatment compliance. Axitinib was not restarted after surgery.

Assessment

History, physical examination, medication list, adverse events and laboratory studies were performed at baseline, and on weeks 3, 7, and 12 after treatment initiation, and then at regular intervals after surgery. A nurse telephoned the patients at weeks 5 and 9 to document AEs.

CT scans of the chest and abdomen were done at study entry, at 7 weeks after axitinib initiation, and at 12 weeks after axitinib initiation. CT scans were evaluated independently by a dedicated genitourinary radiologist who documented the index tumor diameter, and used RECIST to evaluate responses. CT scans at week 7 were obtained just to make sure that patients did not experience tumor progression while on axitinib, and were not used for the primary objective. Per protocol, only CT scans at week 12(prior to surgery) were used for purposes of the primary objective. One patient had 2 tumors in the same kidney and the sum of the longest diameters of these 2 tumors was used for response assessment.

Quality of life was studied using the FKSI-15 (Functional Assessment of Cancer Therapy-Kidney Specific Index-15) questionnaire(6), which was filled at baseline, and on weeks 3, 7, and 12 after treatment initiation, and then at regular follow-up after surgery.

Patients eligible for the trial signed an informed consent. Then, an image-guided percutaneous renal core biopsy was performed by Interventional Radiology to establish a histologic diagnosis.

Patients were scheduled to receive 12 weeks treatment with axitinib, with the last dose being 36 hours prior to surgery. Adverse events were counted using CTCAE version 4.0(7).

Surgery

Following successful completion of neoadjuvant therapy, patients underwent partial or radical nephrectomy (open or laparoscopic at the surgeon's discretion). Primary tumor specimens were immediately sent to pathology on ice for further processing.

Study objectives

The primary objective of the study was to assess the objective response rate (complete and partial responses), using RECIST version 1.1(8), following the administration of axitinib for 12 weeks in patients with locally advanced biopsy-proven clear cell renal cell carcinoma prior to undergoing surgery. Secondary objectives included assessment of the safety, tolerability, and feasibility of axitinib, as well as quality of life while on axitinib in this study population.

Statistical considerations for the primary outcome

A Bayesian design was used to examine the primary endpoint; therefore we calculated 90% credible intervals around the observed proportion of responses and the posterior probability that the proportion of patients who responded to therapy was greater than 20% ($\pi_{ORR} > 0.20$). We would conclude that axitinib was successful in treating patients if the posterior probability that $\pi_{ORR} > 0.20$ was 80% or higher. We assumed that $\pi_{ORR} \sim \text{Beta}(0.4, 1.6)$, which has a mean of 0.20 and a standard deviation of 0.23.

Quality of life

We examined quality of life over time using the FKSI-15 questionnaire. The primary measure for quality of life was total FKSI-15 score. Secondary analyses examined the individual questions on the FKSI-15. Linear mixed models that assumed a random intercept were created to examine FKSI-15 over time.

RESULTS

Patient characteristics

Twenty-four patients were treated with axitinib from May 2011 to April 2013 (Figure 1). All patients had biopsy-proven clear cell RCC prior to starting treatment. Table 1 displays baseline patient characteristics.

Drug treatment

Twenty-two patients completed 12 weeks of axitinib, and one patient completed only 11 weeks of treatment. These 23 patients underwent surgery as planned without delay. Another patient stopped treatment at 7 weeks and was taken to surgery earlier than originally

scheduled. Axitinib dose was titrated up- at least temporarily- in all 24 patients. No patient required decrease of axitinib dose below 5 mg PO BID.

Adverse events

Table 2 shows AEs while on axitinib. No grade 4 or grade 5 AEs were observed. The most common grade 3 AE was hypertension, which was managed medically and did not result in any patient coming off the study early. Common grade 1–2 AEs were fatigue, hoarseness, oral mucositis, hypothyroidism, hand-foot syndrome, nausea and diarrhea. One patient stopped the drug after 11 weeks of treatment, due to grade 3 transient elevation of liver enzymes and thrombocytopenia. Another patient stopped treatment at 7 weeks due to acute kidney injury (with later recovery) and was taken to surgery earlier than originally scheduled. This patient was counted as a failure of treatment.

Response

Median reduction of primary renal tumor diameter was 28.3% (range 5.3–42.9) in the 23 patients with evaluable response at 12 weeks (Figure 2), with 100% of the tumors showing shrinkage. Median tumor diameter per patient changed from 10.0cm (range 4.2–16.6) to 6.9cm (range 2.4–11.6). Eleven of the 24 (45.8%) patients had partial response by RECIST (Figure 3). One had treatment failure (early withdrawal from the study due to AEs), and the rest had stable disease by RECIST. There was no progression of disease while on axitinib. The 90% credible interval for ORR was 0.28 – 0.60. The posterior probability that $\pi_{ORR} > 0.20$ was 0.9966; therefore the primary endpoint of the study was met.

Surgery

Nineteen patients underwent radical nephrectomy (14 open, 5 laparoscopic), while 5 patients underwent partial nephrectomy (all open). Median operative time was 87 minutes (range 56–128) and median estimated blood loss was 225 cc (range 25–3,500). Intraoperatively, no complications or unusual bleeding were encountered. The kidney was noted to be adherent to surrounding tissues in 3 patients, but no surprising or prohibitive effects were noted from being on the study medication. Median length of hospital stay was 5 days (range 3–8). Clear cell RCC was confirmed on final nephrectomy pathology in all 24 patients. Eighteen patients were confirmed pT3a, while 5 were pT1–2 and 1 was pT4 (Table 3).

Postoperative complications

Two patients experienced grade 3 complications. One patient had chylous ascites that required percutaneous drainage without general anesthesia (grade 3a). Another patient had postoperative bleeding, and was taken back to surgery the same day as the original operation (grade 3b). Upon exploration, no source of active bleeding was noted, and the patient recovered well afterwards. Two patients experienced chylous ascites, already had drains placed intraoperatively, and did not require additional surgical/percutaneous interventions. The ascites was self-limited with conservative treatment. Two patients had pulmonary embolism and were treated with anticoagulation. One patient experienced a superficial wound dehiscence (with intact fascia), and was treated with local wound care with excellent recovery. The rest of the postoperative complications are detailed in table 4.

Quality of life

Table 5 (supplemental material) shows the results of the FKSI analysis. FKSI did change over time ($p < 0.0001$), with quality of life worsening in comparison to the screening assessment by week 7 ($p = 0.0004$). However, by week 19, quality of life was not found to be statistically different from screening ($p = 0.3344$). The same pattern was found with energy level, weight, fatigue, and dyspnea. Patients reported worse side effects at weeks 3, 7 and 12 but by week 19 side effects were found to be no worse than at baseline ($p = 0.2568$). Patients were most worried at screening, with continuous improvement at each subsequent assessment ($p = 0.0115$). Patients reported that they did not sleep well, either at screening or at weeks 3, 7 and 12, but by week 19, they had marked improvement in their sleep ($p = 0.0063$). None of the other symptoms (pain, bone pain, enjoyment of life, appetite, cough, fever, ability to work, and blood in urine) changed over time.

DISCUSSION

Since 2008, several agents such as bevacizumab, sorafenib, and sunitinib have been used in the neoadjuvant and pre-surgical setting in patients with their primary renal mass in situ (Table 6, supplemental material). However, most these studies were heterogeneous in several ways: only a few studies were prospective in nature; biopsy-proven clear cell RCC was not always a prerequisite for inclusion in study; most of the studies included either exclusively patients with metastases (stage IV) or a wide range of disease stages; the duration of therapy was not necessarily standardized; and the time off therapy prior to surgery was infrequently predetermined or reported.

In the non-metastatic setting, there are several potential advantages for neoadjuvant targeted therapy in RCC. First, this paradigm can be used to potentially make surgically unresectable tumors resectable. Three studies (9) (10) (11) have investigated sunitinib in patients with surgically complex or unresectable disease, and reported that 3 of 10, 4 of 19, and 13 of 28 patients were rendered surgically resectable after therapy. However, the definition of unresectability is at best very subjective when using preoperative imaging alone. Second, surgical approach can be changed from radical to partial nephrectomy (12) (13). However, the feasibility of partial nephrectomy is also subjective and multifactorial. Third, targeted therapy can be theoretically used prior to resection of renal tumors with inferior vena cava extension. Although several individual case reports (reviewed in (14)) have shown this approach to facilitate surgical resection, this is generally an unreliable approach (14, 15) for downstaging tumors with IVC invasion. Fourth, micrometastatic disease can be potentially destroyed when still microscopic, or when it is still in the early stages before development of additional mutations (16). This is however only a hypothesis, and certainly needs to be studied in prospective clinical trials.

In this study, we prospectively studied for the first time the use of neoadjuvant axitinib in patients with non-metastatic clear cell renal cell carcinoma. We performed pretreatment biopsies in order to focus on patients most likely to benefit from this approach-those with clear cell histology-and in order to avoid treating patients with non-RCC tumors (such as sarcoma, urothelial carcinoma or lymphoma) or non-clear cell RCC, who might have minimal to no chance of response with VEGF-targeting tyrosine kinase inhibitors. All 24

patients enrolled in this study had biopsy-proven clear cell RCC, which was confirmed on final pathological evaluation. Not surprisingly, no patient was found to have pT0 at final pathology.

Patients were treated for a pre-specified period of 12 weeks, in order to achieve maximal benefit from therapy. We have shown previously that most responses occur within 60 days of therapy in the metastatic setting(17), however this duration is unknown in the non-metastatic setting. Since the patients were non-metastatic at presentation, we included restaging studies at week 7 after starting therapy; in order to make sure that no patient developed metastases or progressive disease while on therapy, which would have resulted in taking the patient off the study, and, per protocol, in stopping the study altogether. It was reassuring to see that none of the 24 patients developed progressive disease while on axitinib.

We observed an objective response rate of 45.8% after 12 weeks of preoperative therapy, and a median reduction of primary tumor diameter of 28.3%. This response rate compares favorably with other neoadjuvant and pre-surgical studies with targeted therapy, where objective response rates ranged from 0% to 37%, and median reduction of the primary renal tumor diameter ranged from 7% to 22%. The improved responses in the current study could be related to several factors: First, all the patients had clear cell histology documented with biopsy prior to study entry. This likely selected for patients who are most likely to respond to tyrosine kinase inhibitors. Second, preoperative therapy was given for a period of 12 weeks, which probably maximized the benefit from drug exposure for prolonged periods of time. Third, drug doses were increased on all patients, with the majority of the patients reaching the maximal dose of 10mg twice daily. Fourth, the study agent axitinib, is potentially a more active agent on primary tumors compared to other available targeted therapies in renal cell carcinoma, although this single-arm study is not designed to evaluate any such direct comparisons. Fifth, it is possible that response of the renal primary tumor is different in the non-metastatic setting (as in this study), as compared to the metastatic setting, where most neoadjuvant or pre-surgical studies have been conducted.

Pathological evaluation revealed that 18 patients were stage pT3a, one patient was stage pT4, and 5 patients were stage pT1-T2, knowing that all patients were deemed to be clinical T3a at study entry. While it is possible that upstaging or downstaging could have occurred as a result of the use of axitinib, the study was not designed to look at this specific event, and we believe this discrepancy in staging is likely due to the inaccuracy of clinical staging with the current preoperative imaging modalities utilized in evaluation of patients with renal masses. Five patients were able to undergo partial nephrectomy after 12 weeks of axitinib. Since the conversion of surgery from radical to partial nephrectomy was not a prespecified endpoint in this study, we cannot assume that this conversion to partial nephrectomy was due to the use of axitinib, and this hypothesis will be tested in a different study.

Intraoperatively, no unusual tissue reactions were systematically observed. Postoperative complications were recorded with a validated tool on all patients. We did not note any unusual or unexpected complications that could be attributed to the study drug.

While no grade 4 or 5 adverse events were noted, we did observe a higher AE rate compared to prior studies with axitinib, which were done in the metastatic setting. This is likely related to the duration of therapy with maximal doses used in the majority of patients. Indeed, a recent phase 2 randomized study (18) of dose-titration with axitinib showed that the group of patients who underwent axitinib dose-titration experienced a higher objective response rate, with more adverse events noted. However, progression-free survival was not better in this group, indicating the limited clinical utility of this approach in the metastatic setting. But as the editorialists alluded to (19), this approach could be potentially useful in the neoadjuvant setting though, which is what was performed in our current study. In our study, two patients did not continue the 12-week course of therapy, but all 24 study patients underwent surgery without delay. The AEs were prospectively recorded, and evaluated with frequent clinic visits, as well as phone calls to all patients, in order to rigorously seek and manage these AEs. These AEs were not unusual, and were easily managed with standard care in the Urology clinic setting.

As expected, patients experienced some decline in quality of life while taking axitinib, but most importantly, quality of life was not different at week 19 after drug initiation (which is 6–7 weeks after surgery) when compared to study entry. Interestingly, patient worry levels improved while on the study drug. Patients were able to carry on their daily activities and ability to work while participating in the study, which is quite important given the fact that these patients were eligible for surgery at the start of the study.

For the neoadjuvant approach to be viable in renal cell carcinoma, patients first of all have to experience a major benefit from potentially toxic therapy. But as important, patients should not experience progressive disease or metastases while on therapy, rapid development of metastases after surgery, inability or prolonged delay to undergo surgery, irreversible or grade 4 or 5 adverse events while on therapy, or inability to perform activities of daily living or work while on therapy.

The limitations of our study are the small patient numbers, single-institutional setting, and lack of a control arm. It is unclear at this point if 12 weeks of treatment are necessary for all patients. Further research is needed to elucidate the optimal duration of therapy in the neoadjuvant setting.

CONCLUSIONS

In conclusion, we report the first prospective clinical trial with the tyrosine kinase inhibitor axitinib, conducted exclusively in patients with locally advanced, non-metastatic, biopsy-proven, clear cell renal cell carcinoma, with predefined treatment duration, showing an excellent primary tumor response. We also showed that this approach is feasible and safe at least in the perioperative period, with manageable adverse events while on drug therapy and postoperatively. For the time being, this approach should only be used in clinical trials, or when surgical approaches are not technically feasible, until further studies defining the role of neoadjuvant therapies are conducted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Jose A. Karam has served as a consultant to Pfizer. Nizar M. Tannir has received research funding from Pfizer, and served on the advisory boards of Pfizer. Christopher G Wood has received research funding from Pfizer, served as a consultant to and advisory board of Pfizer.

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PATIENT SUMMARY

In this prospective clinical trial, we found that axitinib, when given prior to surgery, results in significant shrinking of kidney cancers. Larger studies are needed prior to further clinical use.

Figure 1.
CONSORT diagram.

Figure 2. Tumor diameter in centimeters, at 7 weeks and 12 at weeks of treatment. Red indicates partial response, and blue indicates stable disease per RECIST.

Figure 3. Waterfall plot of tumor response in percentages at 12 weeks of treatment. Red indicates partial response, and blue indicates stable disease per RECIST.

Table 1

Baseline patient characteristics

	N	%
Number of patients	24	100
Median age, years (range)	60 (42–83)	
Gender		
Male	19	79.2
Female	5	21.8
ECOG Performance Status		
0	19	79.2
1	5	21.8
Clinical Stage		
T3a	24	100
Clear cell RCC (biopsy)	24	100

Table 2

Drug-related adverse events (CTCAE version 4.0 grading)

Adverse event	All grades, N	All grades, %	Grade 3, N	Grade 3, %
Hypertension	19	79.2	10	41.7
Hoarseness	19	79.2	0	0
Fatigue	18	75.0	1	4.2
Oral mucositis	17	70.8	1	4.2
Hypothyroidism	17	70.8	0	0
Hand Foot Syndrome	15	62.5	1	4.2
Nausea	9	37.5	0	0
Diarrhea	9	37.5	0	0
AST/ALT increase	8	33.3	2	8.3
Sore throat	8	33.3	0	0
Anorexia	7	29.2	0	0
Arthralgia	6	25.0	0	0
Dysgeusia	6	25.0	0	0
Headache	4	16.7	0	0
Myalgias	4	16.7	0	0
Abdominal pain	3	12.5	2	8.3
Gastroesophageal reflux	3	12.5	0	0
Pruritus	3	12.5	0	0
Vomiting	3	12.5	0	0
Weight loss	3	12.5	0	0
Back pain	3	12.5	0	0
Scrotal skin rash	3	12.5	0	0
Acute kidney injury	1	4.2	1	4.2
Thrombocytopenia	1	4.2	1	4.2

Table 3

Surgical and pathological characteristics

	N	%
Number of patients	24	100
Nephrectomy		
Radical	19	79.2
Partial	5	21.8
Surgery		
Open	19	79.2
Laparoscopic	5	21.8
Median operative time, minutes (range)	87 (56–128)	
Median blood loss, cc (range)	225 (25–3,500)	
Pathologic T Stage		
T1a	3	12.5
T1b	1	4.2
T1b	1	4.2
T3a	18	75.0
T4	1	4.2
Fuhrman grade		
2	11	45.8
3	11	45.8
4	2	8.3
Pathologic N Stage		
N0	12	50
Nx	12	50
N1	0	0
Median number of lymph nodes removed (range)	8.5 (1–23)	

Table 4

Postoperative complications (Clavien-Dindo grading(20))

Complication	N	%	Grade
Chylous ascites	3	12.5	3a, 2, 2
Pulmonary embolism	2	8.3	2, 2
Ileus	2	8.3	2, 2
Bleeding	1	4.2	3b
Superficial wound dehiscence	1	4.2	2
Pleural effusion	1	4.2	2
Pneumonia	1	4.2	2
Urinary retention	1	4.2	2
Gastroparesis	1	4.2	2
Anemia	1	4.2	2
Agitation	1	4.2	2