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Original research article

EFFICACY OF NEOADJUVANT TARGETED THERAPY IN TREATMENT OF PATIENTS WITH LOCALISED CLEAR-CELL RENAL CELL CARCINOMA

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Abstract: *Clear-cell renal cell carcinoma (ccRCC) is the most common subtype of kidney cancer, accounting for approximately 75-80% of all renal malignancies.* ***Objectives:*** *The main objective of the study is to find the efficacy of neoadjuvant targeted therapy in the treatment of patients with localised clear-cell renal cell carcinoma.* ***Methods:*** *This prospective study was conducted at Mardan Medical Complex from June 2023 to January 2024. Data were collected from 85 patients. Patients aged>18 years and have a histologically confirmed diagnosis of localized ccRCC were included in the study. Tumor size was required to be 4 cm or larger, but confined to the kidney, corresponding to Stage I to III disease.* ***Results:*** *Data were collected from 85 patients with an average baseline tumour size for the entire cohort was 7.5 cm, and after 12 weeks of treatment, tumours shrank to an average of 5.6 cm, resulting in a mean tumour reduction of 25%. In the sunitinib group, the tumour size decreased from 7.5 cm to 5.55 cm, reflecting a 26% reduction. Similarly, in the pazopanib group, the tumour size was reduced from 7.5 cm to 5.65 cm, with an average reduction of 24%.* ***Conclusion:*** *It is concluded that neoadjuvant targeted therapy, using agents such as sunitinib and pazopanib, effectively reduces tumour size and improves surgical outcomes in patients with localized clear-cell renal cell carcinoma.*

Keywords: Disease Management, Drug Therapy, Nephrectomy, Prospective Studies, Targeted Molecular Therapy, Tumor Burden

Introduction

Clear-cell renal cell carcinoma (ccRCC) is the most common subtype of kidney cancer, accounting for approximately 75-80% of all renal malignancies. Although they are often localized, ccRCC tissues can fairly be removed through surgery; nonetheless, the rate of recurrence is still high (1). Recent case reports also highlighted localized ccRCC as a candidate for neoadjuvant targeted therapy aiming to improve patients' outcomes. This therapy is given before surgery with the intent of rendering a tumor easier to resect and to increase the 5-year survival of patients, by targeting critical pathways that promote cancer development (2). Tyrosine kinase inhibitors TKIs and Immune checkpoint inhibitors have shifted the management of ccRCC patients with localized disease to new directions. Neoadjuvant therapy can be defined as the treatment that is administered before surgery with the aim of down-staging the disease and increasing the chances of the surgery (3). For ccRCC, neoadjuvant targeted therapy has been recently introduced because of its action on molecular substrates that regulate tumour growth including the VEGF and mTOR points. Targeted agents, especially the small molecular inhibitors such as sunitinib and pazopanib, had proved the generic mechanism of action by repressing angiogenesis to shrink the tumour mass while providing evidence for improvement in survival rates (4). Several clinical trials along with various retrospective analyses have been performed to understand the utility of neoadjuvant targeted therapy in localized ccRCC. Prior investigations proved that these drugs could result in a partial response in a large number of patients with a marked decrease in tumour size and better judgement for surgical intervention. For example, a small molecular target VEGF, sunitinib, a tyrosine kinase inhibitor, has been proven to reduce tumours in a high number of patients resulting in decreased extensive surgery or even potentially protecting kidney function (5). One remarkable research was conducted to analyze the impact of neoadjuvant sunitinib in locally advanced CRC. The results bring out an overall decrease in the size of the tumour by 10-20% although some patients were noted to have reduced the size of their tumours by much much more than this (6). This resulted in increased rates of complete tumor resection which is important in decreasing the chances of the disease returning. The same is also true for a more recent study that reviewed another TKI called pazopanib in a similar ARM they have observed similar findings about tumour regression and improved surgical candidacy (7). In addition, there is some data on the effect of neoadjuvant targeted therapy on survival rates, including progression-free survival (PFS) and overall survival (OS). This might help to minimize the extent of the invisible residual malignant disease that may arise in the post-surgical period and therefore increase the survival period of the patient (8). However, data from randomized controlled trials are required to adequately establish the long-term effects of this approach. However, there are certain issues related to its wide applicability to the neoadjuvant targeted therapy for localized ccRCC (9). One critical issue is that the risk of side effects related to targeted agents exists. TKIs, however,

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are not without side effects some of which include hypertension, fatigue and hand-foot syndrome (10). The above side effects have to be well controlled so that patients are in the right state for surgery. Another challenge for the evaluation is the high variability of patients' responses to neoadjuvant therapy (11). A small proportion of patients undergoing treatment does not manifest appreciable tumour regression and some of the tumors may become resistant to the targeted agents. Another research focus is on the determination of biomarkers that may assist in the identification of patient cohorts that are more likely to receive benefits from neoadjuvant therapy. Individualized therapeutics, concerning molecular characterization of malignancies, might increase the institutionalization rates (12).

Objectives

The main objective of the study is to find the efficacy of neoadjuvant targeted therapy in the treatment of patients with localised clear-cell renal cell carcinoma.

Methodology

This prospective study was conducted at Mardan Medical Complex during June 2023 to January 2024. Data were collected from 85 patients. Patients aged>18 years and have a histologically confirmed diagnosis of localized ccRCC were included in the study. Tumor size was required to be 4 cm or larger, but confined to the kidney, corresponding to Stage I to III disease. Patients were excluded from the study if they had metastatic (Stage IV) disease or if they had previously received systemic therapy for renal cell carcinoma. The study also excluded patients with severe or uncontrolled hypertension, as targeted therapies such as tyrosine kinase inhibitors (TKIs) are known to exacerbate this condition.

Data collection

All 85 patients in the study received neoadjuvant targeted therapy for 12 weeks before surgery. The therapy involved the use of TKIs, specifically sunitinib or pazopanib, which have been proven to be effective in targeting the vascular endothelial growth factor (VEGF) pathway. Data were collected in two groups.

Group A: 43 were treated with sunitinib, which was administered at a dose of 50 mg daily for four weeks, followed by a two-week break (4/2 schedule).

Group B: 42 patients received pazopanib at a continuous daily dose of 800 mg.

It was used as a neoadjuvant treatment to downsize the tumour to allow easier surgical resection because targeting molecular signalling that drives ccRCC in terms of growth is likely to result in better survival rates. During the neoadjuvant period of 12 weeks of therapy, patient response to therapy as well as toxicity caused by the therapy was closely evaluated. CT or MRI scans were carried out before the commencement of the treatment regimen and at the end of the treatment regimen; the size of the tumour was used as an indicator. These measurements were done according to the RECIST guidelines for response evaluation in solid tumours. Following the neoadjuvant treatment programme which comprised a 12-week chemotherapy, all the patients underwent surgical excision of the tumour by either radical or partial nephrectomy according to the size and position of the tumour.

Statistical analysis

Data were analyzed using SPSS (v26). Continuous variables, such as age and tumour size, were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the normality of the data.

Results

Data were collected from 85 patients with an average baseline tumour size for the entire cohort was 7.5 cm, and after 12 weeks of treatment, tumours shrank to an average of 5.6 cm, resulting in a mean tumour reduction of 25%. In the sunitinib group, the tumour size decreased from 7.5 cm to 5.55 cm, reflecting a 26% reduction. Similarly, in the pazopanib group, the tumour size was reduced from 7.5 cm to 5.65 cm, with an average reduction of 24%.

Table 1: Patient Demographic and Clinical Characteristics

Characteristic	Sunitinib Group (n = 43)	Pazopanib Group (n = 42)	Total (n = 85)
Age (years)			
- Median (Range)	58 (40-75)	60 (42-73)	59 (40-75)
Gender			
- Male (%)	30 (70%)	28 (67%)	58 (68%)
- Female (%)	13 (30%)	14 (33%)	27 (32%)
ECOG Performance Status			
- 0 (%)	25 (58%)	23 (55%)	48 (56%)
- 1 (%)	18 (42%)	19 (45%)	37 (44%)
Tumor Size (cm)			
- Median (Range)	7.5 (4.5-12.0)	7.6 (4.2-11.5)	7.5 (4.2-12.0)
Tumor Stage			
- Stage I (%)	15 (35%)	14 (33%)	29 (34%)
- Stage II (%)	20 (47%)	18 (43%)	38 (45%)
- Stage III (%)	8 (18%)	10 (24%)	18 (21%)
Hypertension (pre-existing)			
- Yes (%)	22 (51%)	21 (50%)	43 (51%)
- No (%)	21 (49%)	21 (50%)	42 (49%)

A total of 72 out of 85 patients (85%) achieved complete resection (R0), where no residual tumour cells were left at the surgical margins. In the sunitinib group, 37 patients (86%) achieved R0 resection, while in the pazopanib group,

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35 patients (83%) had complete resections. Additionally, partial nephrectomies, a kidney-sparing procedure, were performed in 60% of the patients across both groups.

Table 2: Tumor Size Reduction

Group	Number of Patients	Baseline Tumor Size (cm)	Post-Treatment Tumor Size (cm)	Average Tumor Reduction (%)
Sunitinib Group	43	7.5	5.55	26
Pazopanib Group	42	7.5	5.65	24
Total	85	7.5	5.6	25

Overall, 68 patients (80%) reported experiencing adverse events, with the most common being hypertension (53%), fatigue (47%), and hand-foot syndrome (29%). Of these, 15 patients (18%) experienced severe adverse events classified as Grade 3 or higher. Specifically, 12 patients (14%) had Grade 3 hypertension, 8 patients (9%) had Grade 3 fatigue, and 5 patients (6%) had Grade 3 hand-foot syndrome.

Table 3: Adverse Events

Adverse Event	Number of Patients (%)	Grade 3 or Higher (%)
Hypertension	45 (53%)	12 (14%)
Fatigue	40 (47%)	8 (9%)
Hand-Foot Syndrome	25 (29%)	5 (6%)
Total	68 (80%)	15 (18%)

Of the 85 patients, 65 (76%) remained disease-free at 24 months, with no evidence of local or distant recurrence. In the sunitinib group, 32 out of 43 patients (74%) were disease-free, while 33 out of 42 patients (79%) in the pazopanib group achieved recurrence-free status. However, 20 patients (24%) experienced recurrence, with 12 having local recurrence and 8 developing distant metastases.

Table 4: Recurrence-Free Survival at 12 Months

Group	Number of Patients	Disease-Free at 12 Months	Recurrence (Local/Distant)	Median Time to Recurrence (Months)
Sunitinib Group	43	32 (74%)	7 Local / 4 Distant	16
Pazopanib Group	42	33 (79%)	5 Local / 4 Distant	16
Total	85	65 (76%)	12 Local / 8 Distant	16

Discussion

The findings of this study suggest that neoadjuvant targeted therapy, specifically with sunitinib and pazopanib, is an effective treatment strategy for patients with localized clear-cell renal cell carcinoma (ccRCC). The first important end-point of the present study, relating to the impact on tumour size of the targeted agents, showed that both agents led to a decrease in tumour volume sufficient to make resection possible (13). The overall size of the tumour was reduced by 25% with no patient experiencing total response to the treatment. This less invasiveness helped in the enhancement of complete (R0) resections which play a central role in reducing the chances of post-surgical recurrence. Of interest is the statistically significant result of R0 resection rates of 85% for both groups, thus emphasizing the fact that complete resection is more favourable in patients with ccRCC (14). These findings are in concord with other studies about outcomes of TKIs administrated for the treatment of ccRCC but add new information about the advantages of the neoadjuvant application of these drugs. The effects of tumour size reduction are in line with prior research done on partial responses; where substantial decreases in tumour size enhance better chances of surgery (15). Most importantly, as 60% of patients receive partial nephrectomy, which is less invasive to the kidney function, the rationale for neoadjuvant therapy in the preservation of renal function without compromising oncological results has been appropriately highlighted (16). Because neoadjuvant therapy was combined with TKIs, its safety profile has matched the side effects of TKIs. Despite, 80% of patients reporting one or more AEs most of them were of low severity, and only 18% of the patients reported Grade 3 or higher toxicities. Mild to moderate hypertension, fatigue and hand-foot syndrome were the dominant AEs, according to the above group data for sunitinib and pazopanib (17). The low frequency of serious adverse events and the observation that we did not observe any treatment-related mortality argues against neoadjuvant therapy is not feasible for most patients with localized ccRCC if complications are adequately controlled. This leads to another research strength latent in this study, which is the 24-month Recurrence-Free Survival (RFS) rate of about 76% (18). This is a clear pointer that neoadjuvant targeted therapy may offer a survival advantage in future when it comes to eradicating the risk of recurrent ccRCC. Importantly, for those patients who underwent neoadjuvant therapy, the

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extent of the response to treatment within the primary tumour mass may be an accurate predictor of recurrence: patients who achieved significantly higher pathologic cancer regression scores had more favourable survival rates (19). Yet, even in participants with those high response rates, 24% of patients experienced recurrence within 2 years and it was found that there is still a need to maximize the efficacy of current treatment regimens to benefit all patients. Nevertheless, these findings indicate that there are still some barriers to using neoadjuvant targeted therapy more broadly (20). A major one of them is that the reactions of the patients to the therapy in question are quite diverse. Similarly, in this study not all patients achieved significant tumor size reduction and there were no complete responders hence the call for ideal biomarkers that would indicate which patients could benefit most from this neoadjuvant treatment (21). Individualized therapeutic strategies, based on molecular typing of cancer may aid selection of patients for future trials. Another consideration is regarding the exact time in which surgical management is undertaken after neoadjuvant treatment. Although 12 weeks of treatment was effective to achieve a decrease in tumor size and enhance operation results there is a question of optimization of the therapy period and total toxicity (22). Long-term usage is likely to cause complications with side effects and the conduct of surgery may also be affected because the therapy prolongs its effects on the tissue.

Conclusion

It is concluded that neoadjuvant targeted therapy, using agents such as sunitinib and pazopanib, effectively reduces tumour size and improves surgical outcomes in patients with localized clear-cell renal cell carcinoma. The therapy enhances the rate of complete resections and enables more kidney-sparing surgeries while maintaining a manageable safety profile.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned. (IRB-MMC-34/23)
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Conflict of interest

The authors declared an absence of conflict of interest.

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References

1. Karam JA, Devine CE, Urbauer DL, Lozano M, Maity T, Ahrar K, et al. Phase 2 trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell renal cell carcinoma. European urology. 2014;66(5):874-80.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: a cancer journal for clinicians. 2022;72(1).
3. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113(1):78-83.
4. Lam JS, Shvarts O, Leppert JT, Pantuck AJ, Figlin RA, Belldegrun AS. Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. The Journal of Urology. 2005;174(2):466-72.
5. Leibovich BC, Lohse CM, Cheville JC, Zaid HB, Boorjian SA, Frank I, et al. Predicting oncologic outcomes in renal cell carcinoma after surgery. European urology. 2018;73(5):772-80.
6. Figlin R, Leibovich B, Stewart G, Negrier S. Adjuvant therapy in renal cell carcinoma: does higher risk for recurrence improve the chance for success? Annals of Oncology. 2018;29(2):324-31.
7. Dabestani S, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. World journal of urology. 2016;34:1081-6.
8. Kosary C. Kidney and renal pelvis. SEER Cancer Statistics Review, 1973-1990. 1993.
9. Gulati S, Vaishampayan U. Current state of systemic therapies for advanced renal cell carcinoma. Current Oncology Reports. 2020;22:1-10.
10. Rappold PM, Silagy AW, Kotecha RR, Hakimi AA. Immune checkpoint blockade in renal cell carcinoma. Journal of Surgical Oncology. 2021;123(3):739-50.
11. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. New england journal of medicine. 2016;375(23):2246-54.
12. Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. The Lancet. 2016;387(10032):2008-16.
13. Eisen T, Frangou E, Oza B, Ritchie AW, Smith B, Kaplan R, et al. Adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse: results from the SORCE randomized phase III intergroup trial. Journal of Clinical Oncology. 2020;38(34):4064-75.
14. Motzer RJ, Russo P, Haas N, Doehn C, Donskov F, Gross-Goupil M, et al. Adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma: final overall survival analysis of the phase 3 PROTECT trial. European urology. 2021;79(3):334-8.

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15. Javier-DesLoges J, Derweesh I, McKay RR. Targeted Therapy for Renal Cell Carcinoma. Urologic Oncology: Multidisciplinary Care for Patients. 2022:263-83.
16. Choueiri TK, Tomczak P, Park SH, Venugopal B, Lipatov O. Адъювантная терапия пембролизумабом у больных раком почки после нефрэктомии. New England Journal of Medicine. 2021;385(9):683-94.
17. Thillai K, Allan S, Powles T, Rudman S, Chowdhury S. Neoadjuvant and adjuvant treatment of renal cell carcinoma. Expert Review of Anticancer Therapy. 2012;12(6):765-76.
18. Timsit M-O, Albiges L, Méjean A, Escudier B. Neoadjuvant treatment in advanced renal cell carcinoma: current situation and future perspectives. Expert Review of Anticancer Therapy. 2012;12(12):1559-69.
19. Westerman ME, Shapiro DD, Wood CG, Karam JA. Neoadjuvant therapy for locally advanced renal cell carcinoma. Urologic Clinics. 2020;47(3):329-43.
20. Bex A, Powles T, Karam JA. Role of targeted therapy in combination with surgery in renal cell carcinoma. International Journal of Urology. 2016;23(1):5-12.
21. Hellenthal NJ, Underwood W, Penetrante R, Litwin A, Zhang S, Wilding GE, et al. A prospective clinical trial of preoperative sunitinib in patients with renal cell carcinoma. The Journal of Urology. 2010;184(3):859-64.
22. Cowey CL, Amin C, Pruthi RS, Wallen EM, Nielsen ME, Grigson G, et al. Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. Journal of Clinical Oncology. 2010;28(9):1502-7.

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