Neoadjuvant Targeted Molecular Therapy Before Renal Surgery

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KEYWORDS

• Locally advanced renal cell carcinoma • Neoadjuvant • Partial nephrectomy • Preoperative • Targeted therapy

KEY POINTS

- The purpose of neoadjuvant targeted molecular therapy in patients with renal cell carcinoma is to reduce tumor burden, prevent distant metastases, and increase overall survival.
- In select patients, neoadjuvant therapy offers the possibility of making an unresectable tumor resectable.
- Further investigations are required to determine the role of neoadjuvant therapy in the downstaging of renal cancers with tumor thrombus.
- Neoadjuvant therapy reduces tumor size and complexity, potentially making a partial nephrectomy feasible in cases in which it was originally deemed not possible.
- The use of neoadjuvant therapy in patients with renal cell carcinoma is still being investigated, and it should be used carefully in select patients.

INTRODUCTION

Renal cell carcinoma (RCC) is considered the most lethal of genitourinary malignancies with 62,700 new cases and 14,240 deaths estimated for 2016.[1] The US Food and Drug Administration has approved multiple targeted molecular therapies (TMTs) for advanced RCC during the last decade.[2] Patients with RCC can be diagnosed when still localized (organ-confined RCC), with locally advanced RCC, or with metastatic RCC (mRCC).

The use of neoadjuvant therapies in patients with known metastatic disease is to reduce tumor burden, prevent distant metastasis, and increase overall survival. Multiple randomized controlled trials have shown the efficacy of TMT for advanced RCC.[3–9] Management of locally advanced RCC can be challenging for both urologists and the medical oncologists. In some cases, locally advanced RCC becomes unresectable because of the invasion of adjacent organs, bulky lymphadenopathy, or involvement of vital or critical structures such as mesenteric blood vessels. In these cases, presurgical therapy is used predominantly to reduce tumor size and prevent further local progression. Aggressive surgical resection, when feasible, can render the patient disease free and recurrence free.

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The role of preoperative neoadjuvant therapy in locally advanced and localized RCC remains controversial. Ultimately, larger scale studies, and ideally randomized clinical trials, will be required to explore TMT use not only with regard to primary tumor and venous thrombus downstaging but also in the facilitation of nephron-sparing strategies.

SUMMARY/DISCUSSION

Role of Presurgical Therapy for Renal Cell Carcinoma

Since the approval of TMT for advanced RCC, there have been multiple studies using these agents in various settings, following ineffective prior therapy and as first-line systemic therapy, and largely following prior cytoreductive nephrectomy. A great deal of investigation has attempted to clarify the role of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors in the adjuvant and neoadjuvant settings within the last decade.[10] Although the adjuvant trials to date have not shown any clinical benefit,[11,12] the potential advantages of presurgical treatment extend beyond an overall survival difference. Neoadjuvant TMT has the potential to reduce primary tumor size and complexity, effect primary tumor downstaging, improve surgical outcomes, and decrease perioperative morbidity and mortality.[13]

Initial studies suggested that neoadjuvant TMT, specifically with TKIs, might be the only viable option in the setting of locally advanced RCC if the tumor is unresectable and therefore not amenable to surgery. Although most patients experience some degree of tumor shrinkage, a subset of patients experience cancer progression or a rapid regrowth of tumors after discontinuation of therapy,[14] indicating that routine use is not best practice at the present time. The use of neoadjuvant TMT for mRCC is best reserved for select, heterogeneous settings. The most studied agents in the presurgical setting are sunitinib, pazopanib, sorafenib, and bevacizunimab.[15] Although there are some perioperative issues to consider, including increased bleeding risk and potential for wound-healing issues, in general these agents can be used safely before surgery.[16,17]

To Decrease Tumor Size

Examination of data from prospective phase II studies of TMT for advanced RCC, as well as retrospective analyses of TMT in the presurgical setting, have established a consistent pattern of primary tumor reduction with certain agents (**Table 1**). The effect of sunitinib on the primary tumor in mRCC was first reported in 2008.[18] van der Veldt and colleagues[18] retrospectively analyzed 22 out of 95 patients who had a primary tumor in situ. Seventeen of these 22 patients had an evaluable follow-up computed tomography (CT) scan. Of these 17 patients, 4 (23%) had a partial response, 12 (71%) had stable disease, and 1 (6%) had progressive disease. There was a significant decrease in the volume of the primary tumors (median, 31%; $P = .001$). There was a significant decrease in the volume of the solid part (median, 54%; $P = .001$), whereas the volume of necrosis within the tumor increased significantly (median, 39%; $P = .035$). Three patients (18%) with primary tumors that were initially deemed unresectable underwent nephrectomy because of a decrease in tumor volume. Although this study had some limitations, such as limited follow-up and number of patients, it represented a foundation for prospective research into the effect of TMT in locally advanced and localized RCC.

The MD Anderson group evaluated the primary tumor response in 168 patients treated with TMT for mRCC.[19] Median maximum primary tumor response was −7.1% for patients treated between 2004 and 2009; greater than 30% decrease while on targeted therapy for mRCC is rare. A study by Jonasch and colleagues[20] evaluated the safety and response rates of bevacizumab in the preoperative setting in mRCC. A total of 50 patients were analyzed; 41 (82%) were categorized as intermediate risk and 9 (18%) were poor risk based on the Memorial Sloan Kettering Cancer Center criteria. Forty-five patients were able to undergo restaging scans after 8 weeks of treatment and 23 patients (52%) had some degree of tumor reduction. No patient showed a reduction in primary tumor diameter greater than 30%, but a 10% reduction was seen in 23% of patients using Response Evaluation Criteria in Solid Tumors (RECIST) methodology.

In a retrospective study by Lane and colleagues,[21] 72 potential candidates, including 6 patients who had bilateral tumors, were treated with sunitinib before surgery. Sixty-percent of the patients had nonmetastatic locally advanced RCC and 40% had metastatic disease at baseline evaluation. There was a significant reduction in median tumor size from the initial 7.2 cm (interquartile range [IQR], 5.3–7.8) to the posttreatment size of 5.3 cm (IQR, 4.1–7.5; $P = .0001$). A 32% reduction in tumor area was observed after treatment (IQR, 14%–46%) and a partial response was observed in 15 patients (19%). Sixty-two patients (86%) were able to undergo surgery after treatment.

Based on these studies, the use of neoadjuvant treatment to reduce tumor size is a reasonable expectation, with modest effects on the order of