Efficacy of Pre-surgical Axitinib for Shrinkage of Inferior Vena Cava Thrombus in a Patient with Advanced Renal Cell Carcinoma

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The authors present the first case report of pre-surgical axitinib treatment on primary renal tumor and vena cava thrombus. We report the case of a 78-year-old woman with renal cell carcinoma and inferior vena cava tumor thrombus, successfully downstaged with pre-surgical therapy with axitinib. A significant objective response was observed for tumor size and thrombus. After initiation of axitinib therapy, computed tomography showed a decrease, from 57 to 51 mm, in the maximal renal tumor diameter. The tumor thrombus had shortened to 42 mm and had moved to the inferior hepatic vein (Levels 4–3), thereby obviating the need for thoracotomy. The patient finally accepted surgical treatment. Our case was enabled to perform less surgery for advanced renal cell carcinoma with tumor thrombus using axitinib as a pre-surgical therapy.

Key words: renal cell carcinoma – pre-surgical – molecular target agents – axitinib – IVC thrombus

CASE REPORT

The use of targeted agents in pre-surgical/neoadjuvant therapy for advanced renal cell carcinoma (RCC) was considered to be of particular merit in both preserving renal function and reducing the risk of invasive surgery. However, an advantage in improving overall survival (OS) and progression-free survival (PFS) has not yet been established. Many clinical trials addressing this issue are now ongoing. Cases of pre-surgical and neoadjuvant therapy for advanced RCC using sorafenib, sunitinib and temsirolimus have been reported (1–4). However, reports of axitinib neoadjuvant and pre-surgical therapy for advanced RCC complicated with inferior vena cava (IVC) tumor thrombus are rare. The vascular endothelial growth factor receptor (VEGFR) inhibitor axitinib is considered to be a drug with a high cytoreductive effect. In the pivotal Phase III AXIS trial(5), administration of axitinib in the second-line setting for advanced RCC led to a partial response (PR) rate of 19.6%, a significant improvement over that of sorafenib (9.2%) ($P < 0.001$). In a Japanese trial for patients with cytokine treatment-resistant RCC, axitinib resulted in a PR rate of 57.8% (6). Therefore, axitinib seems to be an effective cytoreductive drug for advanced RCC patients and may be of benefit in treating patients with IVC tumor thrombus in the neoadjuvant/pre-surgical setting.

Here, we report the case of a 78-year-old woman with RCC and IVC tumor thrombus, successfully downstaged with pre-surgical therapy with axitinib, thereby facilitating radical surgery for the RCC and obviating the need for thoracotomy.

A previously healthy 78-year-old woman presented with gross hematuria and European Cooperative Oncology Group performance status 0. Whereas the physical examination findings were unremarkable, abdominopelvic computed tomography (CT) revealed a 57 mm right renal mass with central necrosis. The IVC contained a tumor thrombus (Level 4 in Mayo Clinic classification) located above the diaphragm and below the right atrium (Fig. 1). It did not occupy the entire circumference of the IVC. There were no radiographically visible nodal metastases or distant metastases on CT. Her clinical stage was T3bN0M0 using 2010 AJCC/UICC classification. Nephrectomy and thrombectomy were suggested as primary treatment options. However, the patient was elderly and hence at risk of cardiac arrest. Accordingly, pre-surgical therapy with axitinib (Inlyta®; Pfizer) was recommended to shrink the IVC tumor thrombus. We did not perform a tumor...
biopsy because of the tumor location on the anterior side of the right kidney.

The axitinib dosage and schedule was approved by the Institutional Review Board.

Patient was given a starting dose of 5 mg PO BID. Pre-surgical therapy was administered for 30 days, without the development of Grade 3 or 4 toxicity. Her dose titration was not required.

After initiation of axitinib therapy, CT showed a decrease, from 57 to 51 mm, in the maximal renal tumor diameter. The tumor thrombus (Fig. 2) had shortened to 42 mm and had moved to the inferior hepatic vein (Levels 3–2), thereby obviating the need for thoracotomy.

Four days later, radical surgery was performed for the renal tumor and thrombus with IVC. The operative time was 370 min and the blood loss was 1022 ml. The IVC was reconstructed. There were no complications during or after surgery. Examination of the surgical specimen confirmed significant down staging of the tumor (Fig. 3). The Hematoxylin–Eosin (HE) stain showed the necrosis and hyalinization with residual tumor. The tumor thrombus had necrosis with microvascular change.

**DISCUSSION**

Randomized controlled trials (RCTs) are ongoing worldwide to investigate the efficacy of neoadjuvant/pre-surgical therapy with molecular targeted agents. Currently, evidence from RCTs of a survival benefit with pre-surgical or non-surgical treatment with targeted therapy is lacking.

Before the introduction of axitinib in the clinical setting, clinical trials for neoadjuvant/pre-surgical therapy with other molecular targeted agents were reported. Abel et al. (7) reported a median 7.1% reduction in the maximum primary RCC diameter with molecular targeted agents. However, neoadjuvant/pre-surgical therapy using targeted agents did not
dramatically shrink primary RCC tumors overall. Further, the treatment effect during the first 60 days could predict the long-term curative effect. Cost et al. (8) reported the possibility of minimizing the need for invasive surgery through the reduction of tumor thrombus. Patients with a tumor thrombus received neoadjuvant/pre-surgical treatment with targeted agents for a median of two cycles. The length of the tumor thrombus increased in 28% of patients, no change was observed in 28% of patients, and reduced thrombus lengths were observed in 44% of patients. The level of the tumor thrombus in the IVC increased in 4% of patients (upstaging), decreased in 12% of patients (downstaging) and did not change in 84% of patients. The benefit of neoadjuvant therapy did not seem to extend to OS or PFS. The reported advantage of neoadjuvant/pre-surgical therapy is to preserve renal function and possibly to minimize the need for invasive surgery.

A disadvantage of neoadjuvant/pre-surgical therapy is that some patients may miss the opportunity to receive radical surgery. In addition, adverse events (AEs) associated with molecular targeted agents may become a problem. Chapin et al. (9) reported that the type and severity of AEs depend on the neoadjuvant/pre-surgical therapy used. Use of neoadjuvant/pre-surgical therapy was predictive of having a complication >90 days post-operatively (P = 0.002), of having multiple complications (P = 0.013) and of having a wound complication (P < 0.001). Despite these specific complications, neoadjuvant/pre-surgical therapy was not associated with an increased overall risk of complications in univariate and multivariate analyses (P = 0.064 and P = 0.237, respectively) and was not predictive of severe (Clavien 3) complications (P = 0.625). The outbreak of complications overall was not affected by immediate cytoreductive surgery (univariate analysis, P = 0.064; multivariate analysis, P = 0.237) nor was the incidence of serious (Clavien 3) complications (P = 0.625), thus establishing the perioperative safety of neoadjuvant/pre-surgical therapy using molecular targeted agents.

Axitinib, introduced in 2013, has a higher selectivity for VEGFR and a higher cytoreductive effect than conventional molecular targeted agents. The effectiveness of axitinib compared with sorafenib in the second-line setting for advanced RCC was established in the randomized Phase III study AXIS (5). Not only did axitinib improve PFS (hazard ratio [HR] = 0.664, P < 0.001), but the response rate was significantly higher than that associated with sorafenib (19.6 vs. 9.2%, P < 0.001). The incidence of serious AEs (Grade ≥3) was similar in the treatment arms (49.1 vs. 53.4%).

Tomita et al. (6) reported on the use of axitinib for cytokine treatment-resistant advanced RCC patients. The objective response rate (ORR) was 50% and the clinical benefit rate was 95.3%, as established by the independent review committee. Patients with greater decreases in soluble VEGFR-2 concentrations had a significantly higher ORR and longer PFS than those with smaller decreases (ORR: 64.5 vs. 37.5%, P = 0.045; median PFS: 12.9 vs. 9.2 months, HR = 0.42, P = 0.01).

Karam et al. (10) reported on the use of neoadjuvant axitinib for advanced clear cell RCC (cT2–3bN0M0) in a Phase II trial. Patients were given axitinib for 12 weeks until 36 h prior to surgery. According to the Response Evaluation Criteria In Solid Tumors (RECIST), 46% of patients achieved PR and 54% patients had stable disease (SD). No Grade 4 AEs or intra-operative complications were observed. The authors concluded that axitinib is well tolerated in the neoadjuvant setting in patients with planned surgery for advanced RCC.

Figure 3. Microscopic examination of the tumor: The renal cell carcinomas tissue stained with hematoxylin–eosin was clear-cell renal cell carcinoma as Grade 2 (WHO), pT3b. (a) and (c) HE*200, (b) and (d) HE*400. (c) and (d) Showed the necrosis with residual tumor.
Prior to our report, there have been no cases describing the use of pre-surgical axitinib for advanced RCC patients with a tumor thrombus in the IVC. The diameter of the primary RCC shrunk (57–51 mm; SD according to RECIST), and pre-surgical therapy effectively downstaged the thrombus (Levels–2; shortened to 42 mm), thereby obviating the need for thoracotomy. Blood concentration measurements determined adequate dosage, and there were no severe complications during the perioperative period. Therefore, we recommend the use of neoadjuvant therapy with axitinib for advanced RCC with tumor thrombus.

**Conflict of interest statement**

None declared.

**References**


