Indian J Surg Oncol (June 2012) 3(2):114–119
DOI 10.1007/s13193-011-0100-8

Neo Adjuvant Treatment with Targeted Molecules for Renal Cell Cancer in Current Clinical Practise

Ginil Kumar Pooleri · Tiyadath Balagopalan Nair · Kalavampara V. Sanjeevan · Appu Thomas

Received: 1 September 2011 / Accepted: 21 October 2011 / Published online: 17 November 2011

Abstract Target molecule Treatment (TMT) have emerged as the primary treatment in metastatic renal cell carcinoma. Majority of the patients in pivot trials were post nephrectomy cases. The benefit of cytoreductive nephrectomy in the era of TMT is debated. The role of these molecules in the adjuvant settings and in neo adjuvant/pre surgical role has evoked interest. In this review the different molecules used in the treatment of metastatic renal cancer and its effect on the primary renal tumour is discussed. Information available in the public domain about the presurgical/ neoadjuvant targeted molecular treatment (TMT) is reviewed to understand the benefits and adverse effects of this modality of treatment. Sunitinib and sorafenib are the most commonly used and effective molecules in the neo adjuvant/re surgical treatment of renal cell carcinoma . Bevacizumab is less effective and has more chance of surgical complications in these settings mainly due to poor wound healing secondary to prolonged wash off period . The patent and the surgeon should be aware of the unpredictability and possible adverse effects before advising these molecule pre operatively. The response of the primary renal tumour to the target molecule is different from that of the metastatic tumour. The side effects of the molecules and its effect on the peri operative morbidity and mortality should also be considered when we advise these molecules as pre surgical/neo adjuvant treatment.

G. K. Pooleri (✉)
Uro-Oncology division, Department of Urology,
Amrita Institute of Medical Sciences, AIMS-Ponekkara(PO),
Kochi 41, Kerala, India
e-mail: drginil@gmail.com

T. B. Nair · K. V. Sanjeevan · A. Thomas
Department of Urology, Amrita Institute of Medical Sciences,
AIMS-Ponekkara(PO),
Kochi 41, Kerala, India

Keywords Neoadjuvant · Tyrosine kinase inhibitors · Targeted molecule · Pre surgical · Kidney cancer · RCC

Introduction

Death rates for kidney cancer have been reducing in women by 0.6% per year since 1992 and in men by 1.5% since 2002. This is probably due to the diagnosis of more of early stage cancer. [1] Better knowledge about the renal cancer biology has resulted in the development of new targeted molecules for the treatment of metastatic renal cell carcinoma (mRCC) [2, 3]. Last decade showed a revolutionary advancement in the treatment of metastatic renal cell carcinoma where there was only a limited option earlier. These target molecules have brought up a fresh enthusiasm over the clinical and research fields in the treatment of metastatic renal cell carcinoma even though it is very unlikely that it has made any impact in the cancer mortality.

Targeted Molecules in Advanced Renal Cell Cancer

Two main pathways are utilised in the development of targeted molecular treatment (TMT) of renal cell carcinoma, namely hypoxia-induced pathway which is best utilised in clear cell carcinoma (Bevacizumab, Sunitinib, Sorafenib, Pazopanib, Erlotinib, tivozanib, lapatinib, Tavozanib) [2–12] and Mammalian target of rapamycin (mTOR)pathway in poor risk tumours (eg:Temsirolimus, Evorolimus [2, 14, 15]. The pivot trials of the important molecules are given in Table 1. Sunitinib and Bevacizumab with interferon alfa (IFN α) were the initial molecules that has showed to be effective as the first line management of mRCC [4–7] followed by pazopanib [8]. Sorafenib was found to be

Table 1 Targeted Molecules used in mRCC: the details of the phase III trials

Molecule	Author, Yr	Ph	Design	Rx line	n	PFS (months)	ORR	Nephrectomy	Side effects
Sunitinib	Motzer, 2007 [4, 5]	3	Vs Interferon Alpha	I	375	11Vs 5 HR0.42 (P<0.001)	31%Vs 6%	91%	Diarrhoea
Sorafenib	Escudier, 2007 [9]	3	Vs Placebo	II	903	5.5 Vs 2.8 HR 0.51 (P<0.001)		94%	Dermatological and fatigue
Bevacizumab+IFn α (CALGB 90206)	Rini.BI 2008 [6]	3	Vs Interferon Alfa	I	732	8.5 Vs 5.2 HR;0.71 (P<0001)	25.5% vs 13.1%	85%	Fatigue
Pazopanib	Sternberg 2010 [8]	3	Vs Interferon Alfa	I	435	9.2 v 4.2; HR, 0.46; p<.0001	30%VS 3%	89%	Diarrhoea,,HT hair color changes,
Axetinib	Rini B. I, 2011 [10]	3	Vs Sorafenib	II	723	6.7 Vs 4.7 HR 0.665 (P<0.0001)	19.4% vs9.4%	–	HT, fatigue, dysphonia hypothyroidism
Temsirolimus(Global ARCC Trial)	Hudes G., 2007 [14]	3	Temsiro vs IFnα vs Temsiro+IFnα	poor-prognosis	626	3.8, 1.9,3.7	8.6%, 4.8%, 8.1%	67%	Asthenia, rash, anaemia
Evorolimus	Motzer, 2010 [15]	3	Vs Placebo	II	416	4.9 Vs 1.9 HR 0.33(p<.001)	47% Vs 10%	97%	Infections, dyspnea, fatigue

useful as second line [9]. The results of the recently concluded phase III trial showed significant objective response for Axetinib over Sorafenib when used as second line treatment [10]. Temsirolimus is the most promising molecule for poor prognosis mRCC [14] and evorolimus is studied in patient population who showed progression with other vascular endocthelial growth factor receptor (VEGFR) inhibitors [15]. Combination therapy with different molecules is tried. Sorafenib followed by sunitinib showed some benefit in Progression free survival (PFS), but that of bevacizumab with temsirolimus caused increase in toxicity [16, 17].

Cytoreductive Nephrectomy with TMT

Majority of the patients recruited in major trials of TMT had undergone nephrectomy prior to the treatment [4–15]. Even though cytoreductive nephrectomy has shown benefit in the cytokine era, its role now with targeted molecule has invited a lot of discussion [18, 19]. A recent retrospective analysis showed better outcome with cytoreductive nephrectomy group [20]. Currently two trials are ongoing for the assessment of the usefulness of adjuvant nephrectomy in mRCC [21, 22].

Adjuvant TMT

Targeted molecules are used in adjuvant, neoadjuvant and pre-surgical settings. In the adjuvant settings, the patients with poor risk categories who may have higher chance of local recurrence and micro metastasis is recruited and treated with TMT after nephrectomy. Assure trial (ECOG 2805) was designed to recruit potentially curable patients at the highest risk for recurrence based on existing post-operative nomograms. Either Sunitinib or sorafenib is given to the patients for 1 year and recurrence free survival assessed [23]. S-TRAC and Sorce trial are the other major trials on adjuvant settings that are recruiting patients [24, 25]. The role of adjuvant pazopanib is also being evaluated in renal cancer [26].These trials will give information about the role of the molecules in non metastatic settings.

Neo Adjuvant/Pre Surgical Treatment of Renal Tumour

A clear cut differentiation in the terms, pre surgical and neo adjuvant treatment is not available at present and are used interchangeably. The improved response rate with the new targeted molecules compared with cytokines has evoked interest in using these agents pre operatively. Whether this will transform in improvement of the disease specific survival is the question to be answered [36]. Neo adjuvant treatment with TMT is used in metastatic renal cancer if the primary tumour is large and locally advanced so that the risk of nephrectomy is high or if the surgery is deferred due to the preference of the surgeons or patients or for a clinical study. It may be used in locally advanced tumour to reduce the operative morbidity

Neo adjuvant targeted therapy can be used with following benefits:

1) To reduce the tumour size to make it more amenable to surgery [27–29].
2) To make the tumour amenable to laparoscopic and nephron sparing approaches [28, 29]
3) To improve survival by acting against the micro metastasis and chance of local recurrence in poor prognostic tumours like any other neo adjuvant treatment.

4) To reduce the morbidity by reduction in size and vascularity of the tumour[30, 31]
5) To know the response to the medicine prior to surgery in mRCC [20, 44].
6) To avoid delay in the treatment against clinically active metastasis.
7) for future research by availing tissue to study the effect of medicine in the tumour [25]

Pre surgical/neoadjuvant TMT is used commonly in following conditions.

1) Locally advanced tumours to make the resection possible [25, 26]
2) Mass having large encasing lymph nodes around the hilum where it is difficult to access the renal vessels [46]
3) IVC thrombus [32, 33, 43]
4) In Bilateral or tumours, in solitary kidney and sub normal renal function patients to avoid a renal replacement therapy by possible NSS by size reduction [30, 31].

At present there is no guideline for neo adjuvant TMT in m RCC or locally advanced renal tumours. We should take into consideration the adverse aspects of the treatment before we suggest the neo adjuvant TMT treatment.

1) The response of the primary tumour is unpredictable and may not alter the course of the surgery except in a few cases [34, 36, 43].
2) The adverse effects of the drug can be severe and may need its withdrawal and even postponement of surgery [40, 44]
3) It can cause delayed wound healing, thrombo-embolism, and haemorrhage [30, 36, 40, 44, 45].
4) The financial implications with respect to the limited benefit

Response of Renal Tumour to TMT

In the pivotal studies, majority of the patients who had targeted molecule treatment had pre treatment nephrectomy [4–15].As a result; there is lack of large volume data on the response of the primary tumour to these agents on metastatic set up. Also the degree of response may be different in locally advanced RCC and on the primary tumour of a mRCC [36]. Knowledge of this aspect of tumour response is important to plan pre surgical targeted treatment both in metastatic and in locally advanced tumours. There is report of complete radiological and histological regression of tumour with Sunitinib but the response is very unpredictable [41]. Even though the partial response with Sunitinib in the major trial was 31%, such a response is not seen on the primary tumour or in locally advanced renal tumours with the same agent [4, 36, 43, 46]. The RECIST criteria used in the evaluation of metastatic tumour may not be dependable to assess the response of the primary tumour to the treatment [49].

The response of the renal tumour to the targeted molecular treatments studied in metastatic and in non metastatic settings (Table 2).

The reduction in renal tumour size can make the surgery less morbid. In bilateral tumours and in tumours of solitary kidney, this can be very useful by making the tumour amenable to nephron sparing surgery [31]. Silberstein et al. in an analysis of 12 patients with two bilateral tumours, found that they could plan nephron sparing surgery for all of the patients after pre surgical therapy with TMT .There was median tumour reduction of 1.5 cm (21.1%). Three patients had delayed urine leak [30].

Abel et al. did retrospective analysis of 168 patients with metastatic RCC,who underwent treatment with targeted molecules with the primary tumour in situ it was found that the median maximum tumour response was −7.1% (range −14.1 to −0.1%). Analysis of patients who had multiple radiological evaluation(n:61) it was found that if the response at 60 days of treatment was less than 10% the median maximum response at 154 days was −7.5% compared to 24.5% in patients who had >10% response at 60 days. In this analysis they included patients who were treated with different molecules. Maximum number of patients had treatment with Sunitinib and bevacizumab +/_ erlotinib. Sunitinib(n:75),

Table 2 The response of the renal tumour to the targeted molecular treatments

Author	No	Targeted Treatment	Median Size	Median% reduction	<30% regression of size	Partial response	tumour shrinkage (%patients)
Thomas,AA [35]	19	Sunitinib	10.5	24%	8	3	42%
Hellenthal NJ [38]	20	Sunitinib	7	27.9%	15	2	85%
Silbertein J [30]	14	Sunitinib	7	21%	10	4	100%
Tsunenon Kondo [39]	9	Sunitinib/Sorafenib	–	Range:9–30%	6	3	100%
Abel [36]	168	Multiple Agents	9.6	7.1%	89	10	59%
Lance Cowey [37]	30	Sorafenib	8.7	9.6%	23	2	80%

Erlotinib with bevacizumab(n:25) and pazopenib(n:1) showed tumour response more than 10% . Bevacizumab showed the minimum response median percentage change 0.1%, n 25). Majority of these patients were part of various trials [36].

The same group analysed the data of consecutive 75 patients who had treatment with Sunitinib with tumour in situ with a median follow up of 15 months. They found that if the response was >10% in 60 days of treatment which they called early minor response, then the response was 36.4% compared to the overall response of 10.2% of the group. On multivariate analysis, early minor response was an independent predictor of improved OS (HR: 0.26; p=0.031). Other significant predictors included venous thrombus, multiple bone metastases, lactate dehydrogenase above the upper limit of normal, symptoms at presentation, and more than two metastatic sites [42].

Sorafenib was also evaluated in pre surgical settings. In a pilot study by Cowey et al. the medial response of the primary tumour was 9.6% with a reduction of median diameter from 8.7 to 7.9 cm. Six patients had minimal increase of tumour size. In four patients there were down staging of tumour [37].

The response of the tumour may be different in different tumour types and the tumour may grow in spite of the treatment [50]. Early recognition of the most suitable agent is important. Histopathology, VEGFR expression, in vitro assessment of the tumour response etc. also may have a role in deciding the optimal agent for neo adjuvant treatment [51].

The Carmena trial which is meant to analyse the role of nephrectomy with Sunitinib and the EORTC (SURTIME Trial) which analyse the timing of nephrectomy with Sunitinib will give more information about the response of the primary tumour to neo adjuvant TKI [21, 22].

Neo Adjuvant TMT in IVC Thrombus

The complication rates of surgery in renal tumour with IVC thrombus ranges from 12.4% to 46.9% in patients with level 0–IV tumour thrombi [47]. The reduction in size of the tumour thrombus can cause a reduction in the complication rate. The impact of TMT on the level of renal cell carcinoma vena cava tumour thrombus was studied in a large retrospective analysis by Cost et al. Out of 25 patients, seven had level 3 or 4 IVC thrombus. One patient (4%) had increase and three patients had decrease (12%) in the level of thrombus. All the patients who had reduction in the level of thrombus were treated with Sunitinib. Only in one patient this reduction of level caused any impact on the surgical approach (Level 4 to 3). 21(84%) had stable level. the median reduction was 1.5 cm which may not have an impact on the treatment [43]. Majority of information in literature are case reports of one or two cases [32, 33].Patients and surgeons should be aware that although regression of IVC thrombus is reported, it is rare and occasionally the tumour can even grow in spite of the TMT [34, 43].

TMT can cause reduction in angiogenesis and vascularity of the tumour. Hellenthal et al. showed a decreased contrast enhancement in CT density after sunitinib treatment in 15 of 20 tumours (75%). They suggested that this should be considered as an additional criteria for tumour response [38].This observation is reported with sorafenib also [37]. Kondo et al. observed one major and three minor complications after neo adjuvant treatment mainly haemorrhage [39]. Whether the reduction in size of tumour (1–1.5 cm) and vascularity cause any relative reduction in perioperative complication remains to be answered [36, 43].

Choice of Neo Adjuvant TMT

The optimal agent should be decided considering the response of the tumour, side effects and wash off period required before surgery. The same standard dosage of the medicines in mRCC was used in the neo adjuvant treatment also. Duration is varied from 3 months to more than 1 year [39]. It may be prudent to assess the initial response of the tumour and to give further treatment with the agent only if the response is >10%in the initial 60 days. Even through the duration of pre surgical treatment is not standardised and varied from 2 months to more than 1 year, prescribing the treatment for 5–6 months may cause significant reduction in the tumour if the primary response is good [36, 42]. Sunitinib is the most potent agent which showed the maximum response in neo adjuvant treatment. It caused the maximum reduction in the tumour size and the regression of tumour thrombus [36, 42, 43]. Sorafenib also has given good response on the primary tumour with an additional benefit of minimal peri-operative morbidity [35]. Bevacizumab had the least response [36, 43]. The use of bevacizumab was associated with poor wound healing in 3 out of 52 patients [40]. In a meta-analysis, the incidences of venous thromboembolism among those patients receiving bevacizumab were 11.9% among which 6.3% were high grade particularly of importance if surgery is being planned [45]. Withholding targeted therapy for at least 2 or 3 half-lives before and after surgery may help prevent the adverse effects of these agents on microvasculature and tissue integrity. Sorafenib has the least wash off period as the half life is very short (25 to 48 h) compared to Sunitinib (80 to 110 h) and bevacizumab (11 to 50 days). Also sorafenib may be better tolerated in elderly [48]. Surgery can be undertaken within 3 days of discontinuing the medicine in Sorafenib compared to around 1 week for Sunitinib and further longer in bevacizumab [27, 39, 44].

Conclusion

The response of the primary tumour to the targeted molecular treatment is unpredictable and relatively less compared to the metastatic tumour. Maximum response is reported with sunitinib and sorafenib. If the tumour response is not significant within two months, it is very unlikely to be effective later and is found to be an important prognostic factor in a retrospective analysis. Even though there are case reports of regression of IVC thrombus with TMT, this response may not be significant surgically in majority. Pre surgical/neo adjuvant TMT can cause increased morbidity due to delayed wound healing apart from its specific adverse effects. . The surgeon and the patient must be aware about the possible unpredictable response of the tumour to the targeted medical treatment and the problems and side effects associated with the targeted molecules before it is advised. The trials planned to study the effect of adjuvant TMT and role of nephrectomy with TMT may throw more light on the response of tumour to the molecules. All the present studies are either retrospective analysis or case reports. Prospective studies are required in the neo adjuvant settings to throw more light into these aspects.

References

1. American Cancer Society Cancer Figure and facts 2010: American Cancer Society, Atlanta 2010
2. Ravaud A, Wallerand H, Culine S et al (2008) Update on the medical treatment of metastatic renal cell carcinoma. Eur Urol 54:315–325
3. Carmeliet P, Dor Y, Herbert JM et al (1998) Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature 30:394(6692):485–90
4. Motzer RJ, Hutson TE, Tomczak P et al (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115–24
5. Motzer RJ, Hutson TE, Tomczak P et al (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 27:3584–3590
6. Rini BI, Halabi S, Jonathan E et al (2008) Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 26(33):3584–3590
7. Escudier B, Pluzanska A, Koralewski P et al (2007) Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 370(9605):2103–11
8. Sternberg CN, Davis ID, Mardiak J et al (2010) Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 28:1061–1068
9. Escudier B, Eisen T, Stadler MW et al (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125–34
10. Rini BI, Escudier B, Tomczak P et al (2011) Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): Results of phase III AXIS trial. J Clin Oncol 29: (suppl; abstr 4503) 2011 ASCO Annual Meeting Abstract No: 4503
11. A Study of Tivozanib (AV-951), an Oral VEGF Receptor Tyrosine Kinase Inhibitor, in the Treatment of Renal Cell Carcinoma http://clinicaltrials.gov/ct2/show/NCT00502307. Accessed on 15th August 2011
12. A Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects With Advanced Renal Cell Carcinoma (TIVO-1) http://clinicaltrials.gov/ct2/show/NCT01030783. Accessed on 15th August 2011
13. Gordon MS, Hussey M, Nagleet RB et al (2009) Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. J Clin Oncol 27:5788–5793
14. Hudes G, Carducci M, Tomczak P et al (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271–81
15. Motzer RJ, Escudier B, Oudard S et al (2010) Phase 3 trial of everolimus for metastatic renal cell carcinoma final results and analysis of prognostic factors. Cancer 116:4256–65
16. Porta C, Procopio G, Cartenì G et al (2011) Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases. BJU Int. May 23. doi: 10.1111/j.1464-410X.2011.10186.x. [Epub ahead of print]
17. Negrier S, Gravis G, Perol D, et al : Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. The Lancet Oncology12 (7): 673–680, 2011.
18. Coppin C, Porzsolt F, Autenrieth M, Kumpf J et al (2008) Immunotherapy for advanced renal cell cancer (Review) Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library, Issue 4 http://www.thecochranelibrary.com, accessed August 15th
19. Biswas S, Kelly J, Eisenet T et al (2009) Cytoreductive nephrectomy in metastatic clear-cell renal cell carcinoma: perspectives in the tyrosine kinase inhibitor era. The Oncologist 14:52–59
20. Choueiri TK, Xie W, Kollmannsberger C et al (2011) The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol 185:60–6
21. Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) NCT00930033 Link:http://clinicaltrials.gov/ct2/show/NCT00930033: Accessed August 15th 2011
22. Immediate surgery or surgery after sunitinib malate in treating patients with metastatic kidney cancer, EORTC 30073 Link: http://clinicaltrials.gov/ct2/show/NCT01099423?term=EORTC+30073&rank=1: Accessed August 15th 2011
23. Sunitinib or sorafenib in treating patients with kidney cancer that was removed by surgery NCT00326898 Link http://www.clinicaltrials.gov/ct/show/NCT00326898?order%20=%201: Accessed on August 15th 2011
24. S Trac Trial Link: http://www.clinicaltrials.gov/ct/show/NCT00375674?order%20=%204 (Accessed on 4th Aug 2011)
25. Sorce trial Link: www.ctu.mrc.ac.uk/news_and…/sorce_update_12102007.aspx(Accessed on 4th Aug 2011)
26. A study to evaluate pazopanib as an adjuvant treatment for localized renal cell carcinoma (RCC) (PROTECT) NCT01235962 Link:http://clinicaltrials.gov/ct2/show/NCT01235962 Accessed on 4th Aug 2011
27. Thomas AA, Rini BI, Stephenson AJ et al (2009) Surgical resection of renal cell carcinoma after targeted therapy. J Urol 182:881–886
28. van der Veldt AAM, Meijerink MR et al (2008) Sunitinib for treatment of advanced renal cell cancer: primary tumor response. Clin Cancer Res 14:2431–2436

29. Amin C, Wallen E, Pruthi RS et al (2008) Preoperative tyrosine kinase inhibition as an adjunct to debulking nephrectomy. Urology 72(4):864–8
30. Silberstein JL, Millard F, Mehrazin R et al (2010) Feasibility and efficacy of neoadjuvant Sunitinib before nephron-sparing surgery. BJU Int 106:1270–1276
31. Ansari J, Doherty A, McCafferty I et al (2009) Neoadjuvant sunitinib facilitates nephron-sparing surgery and avoids long-term dialysis in a patient with metachronous contralateral renal cell carcinoma. Clin Genitourin Cancer 7:39–41
32. Karakiewicz PI, Suardi N, Jeldres C et al (2008) Neoadjuvant sutent induction therapy may effectively down-stage renal cell carcinoma atrial thrombi. Eur Urol 53:845–8
33. Karnes RJ, Blute ML (2008) Surgery insight: management of renal cell carcinoma with associated inferior vena cava thrombus. Nat Clin Pract Urol 5:329–39
34. Bex A, van der Veldt AA, Blank C et al (2010) Progression of a caval vein thrombus in two patients with primary renal cell carcinoma on pretreatment with sunitinib. Acta Oncol 49:520–523
35. Thomas AA, Rini BI, Lane BR et al (2009) Response of the primary tumor to neoadjuvant sunitinib in patients with advanced renal cell carcinoma. J Urol 181:518–523
36. Abel J, Culp SH, Tannir NM et al (2011) Primary tumor response to targeted agents in patients with metastatic renal cell carcinoma. Eur Urol 59:10–15
37. Cowey CL, Amin C, Pruthi RS et al (2010) Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. J Clin Oncol 28:1502–1507
38. Hellenthal NJ, Underwood W, Penetrante R et al (2010) Prospective clinical trial of preoperative sunitinib in patients with renal cell carcinoma. J Urol 184:859–864
39. Kondo T, Hashimoto Y, Kobayashi H et al (2010) Presurgical targeted therapy with tyrosine kinase inhibitors for advanced renal cell carcinoma: clinical results and histopathological therapeutic effects. Jpn J Clin Oncol 40(12):1173–1179
40. Jonasch E, Wood CG, Matin SF et al (2009) Phase II presurgical feasibility study of bevacizumab in untreated patients with metastatic renal cell carcinoma. J Clin Oncol 27:4076–4081
41. Robert G, Gabbay G, Bram R et al (2009) Complete histologic remission after sunitinib neoadjuvant therapy in T3b renal cell carcinoma. Eur Urol 55:1477–1480
42. Abel EJ, Culp SH, Tannir NM et al (2011) Early primary tumor size reduction is an independent predictor of improved overall survival in metastatic renal cell carcinoma patients treated with sunitinib. Eur Urol. doi:10.1016/j.eururo.2011.07.008 (Published online ahead of print on July 14, 2011)
43. Cost NG, Delacroix SE Jr, Sleeper JP et al (2011) The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. Eur Urol 59:912–918
44. Bessede T, Pignot G, Patard JJ et al (2011) Safety issues and rationale for neoadjuvant approaches in renal cell carcinoma geraldine. Eur Urol. doi:10.1016/j.eururo.2011.06.003, Article in press
45. Nalluri SR, Chu D, Kereszteset R et al (2008) Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients a meta-analysis. JAMA 300(19):2277–2285
46. Amin C, Wallen E, Pruthi RS et al (2008) Preoperative tyrosine kinase inhibition as an adjunct to debulking nephrectomy. Urology 72:864–868
47. Karnes RJ, Blute ML (2008) Surgery insight: management of renal cell carcinoma with associated inferior vena cava thrombus. Nat Clin Pract Urol 5:329–39
48. Eisen T, Oudard S, Szczylik C et al (2008) Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. J Natl Cancer Inst 100:1454–1463
49. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–47
50. Rini BI, Atkins MB (2009) Resistance to targeted therapy in renal-cell carcinoma. Lancet Oncol 10(10):992–1000
51. Sunitinib before and after surgery in treating patients with metastatic kidney cancer that can be removed by surgery: http://www.clinicaltrials.gov/ct2/show/NCT00747305?term=sunitinib+and+RCC&rank=37. Accessed on 30th Aug 2011