The emerging role of targeted therapy in renal cell carcinoma (RCC): Is it time for a neoadjuvant or an adjuvant approach?

Alessandro Sciarra*, Susanna Cattarino, Stefano Salciccia, Andrea Alfarone, Alessandro Gentilucci, Ulderico Parente, Gianna Mariotti, Michele Innocenzi, Vincenzo Gentile

Department of Urology “U. Bracci”, University Sapienza of Rome, Viale Policlinico 155, 00161 Rome, Italy

Accepted 11 February 2011

Abstract

Purpose: We address whether rational and significant clinical data exist on using angiogenic targeted therapies as neoadjuvant or adjuvant options to nephrectomy in non-metastatic RCC.

Methods: We reviewed the recent international literature by carrying out a PUBMED search.

Results: Neoadjuvant: a possible indication for a neoadjuvant targeted therapy approach is to facilitate surgery, reducing risks for patients and increasing the possibility of removing the mass and improving oncological results. Adjuvant: three major phase III clinical trials are currently ongoing. The ASSURE trial (1 year on oral sunitinib, sorafenib or placebo), the SORCE trial (3 years on placebo versus 1 year on sorafenib, followed by 2 years on placebo versus 3 years on sorafenib), and the S-TRAC trial (1 year on sunitinib or placebo) analyze patients who are at high risk of relapse.

* Corresponding author. Tel.: +39 3333977820.
E-mail addresses: sciarra.md@libero.it, sciarrajr@hotmail.com (A. Sciarra).

Conclusions: Rationale and needs for the neoadjuvant or adjuvant use of targeted therapies in RCC are relevant. Significant phase III trials on the adjuvant use of targeted therapy in RCC are ongoing.

Keywords: Renal cell carcinoma; Targeted therapy; Nephrectomy; Sorafenib

1. Introduction

The incidence of renal cell carcinoma (RCC) has been increasing over the past few decades. In the USA, more than 38,000 new cases and 12,000 deaths from RCC were estimated to occur in 2006 [1]. The diagnostic trend is mainly due to the use of non-invasive imaging procedures, which detect incidental renal tumors. The majority of incidentally detected RCC are at a low stage.

Medical treatment options for advanced RCC have been limited in the past because of tumor resistance to chemotherapy and radiotherapy. The immunogenicity of RCC has represented the basis of immunotherapy in advanced RCC. Administration of interferon (IF) or interleukin-2 (IL-2), or their combination, however, has resulted in the modest improvement in survival and only a limited subgroup of RCC can benefit from immunotherapies [2,3]. In the last few years, new advances have begun to change the management of RCC. A series of new approaches, called “targeted therapy”, are revolutionizing the treatment of RCC. Several phase II and phase III trials [4–7] using strategies to inhibit vascular endothelial growth factor (VEGF), other angiogenic factors, or the mammalian target of the rapamycin (mTOR) system, have demonstrated significant anti-tumor effects in the management of RCC. As research into the molecular basis of RCC continues, the options available to the clinician for the treatment of advanced RCC will continue to expand [8,9].

Several guidelines, emphasizing that targeted therapies are currently recommended only for the metastatic stage of RCC (mRCC), have been provided.

The present review in particular will address whether rational and significant clinical data exist on using angiogenic targeted therapies as neoadjuvant or adjuvant options to nephrectomy in the treatment of non-metastatic RCC.

2. Methods for the review

We reviewed the recent international English-language literature using PUBMED search (keywords: non-metastatic RCC; targeted therapy; neoadjuvant; adjuvant); referring in particular to recent literature (2007–2010) and to articles published only in international journals. In particular we focused our research on the following questions:

- What are the indications for patient selection for neoadjuvant or adjuvant therapies?
- Which kind of clinical data (case reports, phase II or phase III trials) currently support these indications?

3. Results of the review

3.1. Do a rationale and a need for neoadjuvant or adjuvant therapies exist?

Renal cell carcinoma remains one of the most lethal of the genito-urinary cancers. Targeted agents such as sorafenib, sunitinib, bevacizumab and temsirolimus have demonstrated substantial improvement in the objective response rate and progression-free survival in patients with advanced RCC [4,6,7,10]. However, targeted therapies are not curative and integration of surgery with these therapies represents the best treatment in patients with advanced RCC [11].

Also, the EAU guidelines [12] recommend nephrectomy in cases of metastatic disease when patients are both suitable for surgery and have a good performance status, so that significantly better results can be obtained from systemic therapies.

However, the real advantage that surgery can produce together with targeted therapies for metastatic RCC will be defined only at the conclusion of ongoing specific clinical trials.

Nephrectomy provides curative treatment for localized disease, but unfortunately, 30% of patients subsequently experience recurrence and metastasis [13,14].

Results available on targeted therapies for metastatic RCC so far have demonstrated a greater effect of these therapies on metastatic sites than on the primary tumors. However, different large phase III trials [6] have also reported primary tumor shrinkage after targeted therapies; smaller phase II trials [15] on neoadjuvant targeted therapies also reported a variable but in some cases significant shrinkage of the primary tumor.

Randomized clinical trials will enable patients to be identified and offered neoadjuvant or adjuvant therapies for optimal management with accurate preoperative and postoperative risk stratification.

The significant rate of patients who develop progression after surgery, despite the initial nonmetastatic stage of RCC, supports the need for adjuvant therapy.

Does a rationale exist for the use of targeted therapies as neoadjuvant or adjuvant support to surgery, not only in the advanced stages but also in nonmetastatic RCC?

Such a rationale is sustained by the following points:
(A) Targeted therapies used in RCC produce an objective response rate of up to 40% and up to 75% of patients experience a reduction in tumor burden [11,16].

The main targeted therapy in RCC is aimed at angiogenesis and the VEGF signaling pathway. Bevacizumab is a recombinant human antibody against VEGF binds. In RCC bevacizumab acts through three potential mechanisms: (1) regression of microvasculature; (2) normalization of mature vasculature; and (3) inhibition of the production of new vasculature [15].

Sunitinib is a multi-targeted receptor tyrosine-kinase inhibitor. In RCC sunitinib may display an anti-tumor effect through anti-angiogenic effects against VEGF receptor and platelet-derived growth factor (PDGF) receptor [16].

Sorafenib is an oral multikinase inhibitor that was originally developed because of its capacity to inhibit the Raf system and several tyrosine kinases that regulate cell proliferation and angiogenesis. The relevant role of the Raf kinase pathway on RCC pathogenesis has been clearly demonstrated in preclinical studies [17]. It has been suggested that, in RCC, sorafenib inhibits tumor growth by a duel mechanism of action: either directly on the tumor (Raf signaling) and/or indirectly on tumor angiogenesis (VEGFR and PDGFR signaling) [18]. However, the relevance of Raf inhibition by sorafenib activity in RCC is currently unknown.

Temsirolimus and everolimus are mTOR inhibitors and antagonize cell growth and proliferation by disrupting intracellular signaling pathways. Furthermore, mTOR inhibitors block hypoxia-inducible factors (HIF), which drives the downstream regulation of several pro-angiogenic factors [19].

Therefore in RCC, all these targeted therapies, either through a direct anti-tumor effect or indirectly by inhibiting angiogenesis, can produce a tumor mass shrinkage and can reduce the risk of local and distant progression.

This first point represents a strong rationale for the use of these targeted therapies neoadjuvant or adjuvant to surgery.

(B) Several prognostic models and nomograms have been developed to estimate outcomes of patients with RCC, either in the non-metastatic or in the metastatic stage [20]. In terms of neoadjuvant therapy it is not possible to define risk such as for adjuvant therapy: risk factors justifying neoadjuvant therapy could be clinical settings in which there is a high risk during the surgical procedure of obtaining radical removal of the tumor. More specifically, for the adjuvant strategy, factors influencing prognosis can be classified into: anatomical, histological, clinical, and molecular. Models such as the UCLA Integrated Scoring System (UISS) or the Leibovich or Mayo Clinic (SSIGN) system, combining independent prognostic factors, can be more accurate than TNM staging or Fuhrman grades alone for predicting survival or risk of progression after surgery [12].

The UISS model was developed to predict overall survival in patients with kidney cancer regardless of histological subtype, whereas the SSIGN model was developed to predict cancer-specific survival in patients with clear cell RCC only. The Mayo group further developed a model distinct from the SSIGN to predict disease-free survival in patients with non-metastatic clear cell RCC, referred to as the Leibovich prognostic score [21,22].

These prognostic scores can select RCC cases that, despite being at a non-metastatic stage, are at high risk of progression using nephrectomy as the primary treatment.

(C) Radical nephrectomy is the gold standard treatment for nonmetastatic RCC.

In recent years an increased interest has been directed at reducing the aggressiveness of surgery for RCC. Laparoscopic nephrectomy has become an established surgical procedure worldwide. The laparoscopic approach can duplicate open surgery and oncological principles, reducing the invasiveness and the morbidity of surgery for the patient. EAU guidelines [12] consider laparoscopic nephrectomy a standard of care for patients with T1-2 RCC and possibly also for T3a tumors in experienced hands.

The same EAU guidelines underline the fact that adrenalectomy during nephrectomy, except in the case of large upper pole tumors, can be spared. Moreover, extended lymphadenectomy does not improve survival in patients without clinically detectable lymph nodes, and it should be restricted to staging purposes in palpable and CT-detected enlarged lymph nodes [12].

Nephron-sparing surgery is an established curative approach for the treatment of RCC, but tumor size is a crucial parameter for the choice of this surgical option [12].

Currently, patients not suitable for surgery because of a poor performance status, should be considered for nonsurgical alternative techniques such as radiofrequency ablation, cryoablation, microwave ablation, laser ablation and high-intensity focused ultrasound ablation. In these cases, tumor size is also a crucial factor and only smaller peripheral tumors can be successfully treated.

The actual kidney surgery, therefore, tries to reduce invasiveness and morbidity for patients; to do this, tumor size is the main factor for an oncologically correct approach.

3.2. Indications for neoadjuvant therapy

The aim of neoadjuvant therapies is: (1) to facilitate surgery, reducing risks for patients and increasing the possibility of removing the mass and (2) to improve oncological results in terms of risk of progression and survival (if neoadjuvant therapy improves the possibility of radical surgery, oncological results could also improve).

Neoadjuvant therapies are commonly used to downstage locally advanced tumors and to improve survival.

In patients with RCC, neoadjuvant studies have been limited during the cytokine era because of the poor responses in the primary tumor and the significant toxicity associated with treatment [23].

The introduction of targeted therapies can produce new interest and a valid rationale to analyzing a neoadjuvant approach to RCC. Targeted therapies have higher response rates in the primary tumors (tumor shrinkage) and a favorable safety profile.

We tried to identify which possible indications might be particularly suitable for a neoadjuvant course of targeted therapy.

Three possible clinical settings are described: (1) patients with an imperative indication for nephron-sparing surgery; (2) patients with high-volume RCC; and (3) patients with extended vena cava thrombus.

3.2.1. Case number 1
3.2.1.1. Presentation of a patient with absolute indications for nephron-sparing surgery.

- A 69-year-old man with gross hematuria.
- No other significant clinical conditions or significant medical history.
- CT of the abdomen revealed a 7.5-cm left-sided renal mass and a 5.0-cm right-sided medial renal mass.
- The patient was considered for a right-sided nephrectomy and left-sided nephron-sparing surgery.
- In the post-operative setting the patient required blood transfusion and he experienced an acute increase in creatinine values (Fig. 1).

As also indicated by the EAU guidelines [12], nephron-sparing surgery for RCC, when performed as an elective indication in patients with a solitary tumor measuring <4 cm in its maximum diameter, provides recurrence-free and long-term survival rates similar to those observed after a radical surgical procedure (Fig. 2). Moreover, in these elective cases, there is some evidence that radical nephrectomy carries an increased risk of impaired renal function compared with nephron-sparing surgery [24]. Tumor size is the main factor influencing indications for and results of nephron-sparing surgery. EAU guidelines [12] recommend this approach for tumors measuring <4 cm in the maximum diameter, but also for tumors measuring 4–7 cm in centers with expertise.

Nephron-sparing surgery carried out for absolute indications is often performed on tumors with larger diameters and it is associated with increased complication rates and higher rates of developing a locally recurrent disease [25].

In case number 1, the indication for a neoadjuvant targeted therapy approach is to reduce kidney tumor size and therefore to consent to a better approach to the nephron-sparing technique. Reducing tumor size, targeted therapies may also be...
effective in reducing morbidity and risk of local recurrence in absolute indications for nephron-sparing surgery.

In the literature, some case reports describe the use of targeted therapies as neoadjuvant to an absolute indication for nephron-sparing surgery, obtaining downstaging of the tumor enough to allow conservative surgery [26].

3.2.2. Case number 2
3.2.2.1. Presentation of a patient with a renal mass associated with a vena cava thrombus.

- A 71-year-old man with gross hematuria and abdominal pain.
- CT/MRI of the abdomen revealed a solid mass (8.0 cm in diameter) at the left kidney level associated with a thrombus in the inferior vena cava.
- The patient was considered for a left nephrectomy and thrombectomy.
- In the post-operative setting the patient required blood transfusions and he experienced an acute increase in creatinine values (Fig. 3).

Renal cell carcinoma invades the venous system to different degrees in 4–9% of cases [27] and can extend into the renal vein or the inferior vena cava (IVC; Level I), above the diaphragm (Level II) or into the atrium (Level III).

Several studies [28,29] underlined the fact that tumor characteristics, not the level of thrombus, determine the prognosis. However, the level of thrombus affects the surgical approach and the need for a bypass technique. A Level II and Level III thrombus leads to longer surgery, higher peri-operative morbidity and complications. Five-year survival rates for nonmetastatic RCC with tumor thrombus range from 20% to 70% if the thrombus is completely removed [30]. Tumor thrombus is not associated with an adverse prognosis, when a complete surgical resection is possible.

Radical nephrectomy with thrombectomy is the treatment of choice in patients with IVC involvement. For Level III thrombosis a cardiopulmonary bypass has been used as an adjunct to removing cavo-atrial tumor thrombus. For Level II disease, veno-venous bypass can be a useful technique. Other intra-operative techniques include hypothermic circulatory arrest, hypotensive anesthesia, and colloid administration [31].

To reduce surgical invasiveness and risk of peri-operative morbidity, patients with an RCC associated with Level II or Level III thrombus could be candidates for neoadjuvant targeted therapies, so as to reduce thrombus extension.

In the literature, different case reports [23,32,33] describe a significant reduction in IVC thrombus extension after neoadjuvant treatment using sorafenib or sunitinib. In some cases [32], after 3–6 months of neoadjuvant treatment, a Level II and Level III thrombus was found at surgery limited to the renal vein, with a massive substitution by necrotic tissue (Fig. 4). This kind of result can also have oncological advantages, but in particular significantly reduce surgical aggressiveness and related complications.

3.2.3. Case number 3
3.2.3.1. Presentation of a patient with a voluminous renal mass medically considered too high risk for surgery.

- A 69-year-old obese man with gross hematuria.
- Medical history of atrial fibrillation, diabetes, and cerebrovascular accident.
- CT of the abdomen revealed a 10-cm, upper pole, left-sided renal mass with suspected peri-renal fat invasion and straight contiguity with the colon.
The patient was considered for left nephrectomy associated with a high level of anesthesiological risk.

Significantly long operative time and blood loss.

In the post-operative setting the patient developed cardiac ischemia and experienced an acute increase in creatinine values.

When massive involvement of the kidney and peri-renal structures occurs from an RCC, surgery is the primary option. However, the considerations for less invasive surgery, or for a laparoscopic approach, are not realistic. In these cases nephrectomy becomes a major surgical procedure associated with a significant risk of morbidity (11–40%) [34]. Alternative conservative management strategies (cryoablation and radiofrequency) are highly influenced by tumor size and are generally restricted to small tumors of <5 cm in diameter [12]. Moreover tumor extension and local stage significantly influence the prognosis of RCC patients [12]. Nephrectomy in a T3 or T4 RCC may not really represent a radical treatment and these cases could be associated with a significant risk of local progression [12].

In case number 3 the indication for a neoadjuvant targeted therapy approach is to significantly reduce RCC sizes and the possibility of peri-renal infiltration in order to: (1) perform an easier nephrectomy and (2) oncologically improve results obtaining a better radical nephrectomy.

The rationale and the need for neoadjuvant therapy exist in the cases we presented. Phase III trials should be performed, demonstrating the advantage in terms of surgical procedure between neoadjuvant plus surgery versus surgery alone.

Some phase II studies [11] analyzed a neoadjuvant targeted therapy approach in “unresectable” locally advanced RCCs. The University of North Carolina [15] analyzed cases with locally advanced RCC treated with targeted therapy before nephrectomy, in a phase II study. The cases were surveyed for the effect of therapy on tumor burden, surgical approach, and timing. Sorafenib and sunitinib were used for >4 weeks before nephrectomy. Most patients were initially considered to have unresectable disease because of the bulk of local disease, or because at diagnosis they had another contraindication for surgery. Nephrectomy was performed a minimum of 2 days after cessation of targeted therapy. The surgical approaches included open or laparoscopic radical nephrectomy. They reported no increases in the operative time (mean 195 min). Targeted therapies did not seem to have a meaningful detrimental effect on the operation, either in terms of blood loss or intra-operative and post-operative complications. A mean decrease in tumor size of 12.9% after targeted therapy was described using the Response Evaluation Criteria in Solid Tumors (RECIST). The responses in the primary tumor were quite varied, ranging from 0.8% to 54% (RECIST). Because of the reduction in tumor size and the substantial reduction in the lymphadenopathy, these patients were able to undergo a complete resection of all disease. With their initial diagnosis, these RCC cases would have had to undergo surgery in which it would have been difficult to achieve complete clearance. In contrast, they were free of recurrence for >1 year after nephrectomy [15].

A second phase II study was developed by Cleveland Cancer Institute [11], particularly focusing on a surgical approach after the use of targeted therapies. In a previous experiment they used sunitinib as neoadjuvant therapy for locally advanced RCC, showing 42% of cases with demonstrated tumor shrinkage. In a second experiment they analyzed the use of sorafenib, sunitinib or bevacizumab plus IL-2 as neoadjuvant therapy in unresectable RCC. A median of four cycles of therapy was administered. Surgical resection included open and laparoscopic approaches and also partial nephrectomy. Authors reported a median hospital stay of five days (range 1–12) and 5% and 16% mean intra-operative and postoperative complication rates, respectively. Only two cases showed major peri-operative complications: the patients first underwent partial liver resection resulting in extensive hemorrhage; the second also underwent a bowel resection resulting in anastomotic bowel leak.

A third phase II study was developed by the M.D. Anderson Cancer Center [35] focusing on the use of bevacizumab as a pre-surgical treatment in patients with metastatic RCC. In this phase II trial, 50 patients received bevacizumab plus erlotinib or bevacizumab alone for 8 weeks followed by restaging. Median progression-free survival was 11.0 months and median overall survival was 25.4 months. Two perioperative deaths occurred, which were not attributable to the treatment. Wound dehiscence resulted in treatment discontinuation for three patients and treatment delay for two others.

These and other experiences showed that targeted agents are generally well tolerated and do not increase surgical morbidity during nephrectomy.

To address these results several precautions should be used [11]: (1) withholding targeted therapy for at least 2–3 half lives before and after surgery to prevent adverse events on microvasculature and tissue integrity; (2) using meticu-

Fig. 4. CT of the abdomen revealing a voluminous renal mass with suspected peri-renal fat invasion and straight contiguity with the colon.

Table 1  
Targeted therapy in RCC phase II trials: neoadjuvant treatment.

<table>
<thead>
<tr>
<th>Study title</th>
<th>Clinical trial identifier</th>
<th>Target accrual</th>
<th>PI (country)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib in treating patients undergoing surgery for stage II, stage III, or stage IV RCC</td>
<td>NCT00405366</td>
<td>30</td>
<td>Rathmel (USA)</td>
</tr>
<tr>
<td>A phase II neoadjuvant clinical trial to evaluate the efficacy of sorafenib in metastatic RCC</td>
<td>NCT00126659</td>
<td>45</td>
<td>Jonasch (USA)</td>
</tr>
<tr>
<td>Pre-operative administration of sorafenib in patients with metastatic RCC undergoing cytoreductive nephrectomy</td>
<td>NCT00480389</td>
<td>30</td>
<td>Finelli (Canada)</td>
</tr>
<tr>
<td>Neoadjuvant clinical trial to evaluate the efficacy of bevacizumab for RCC</td>
<td>NCT00113217</td>
<td>50</td>
<td>Jonasch (USA)</td>
</tr>
<tr>
<td>Sunitinib before and after surgery in treating patients with metastatic RCC that can be removed by surgery</td>
<td>NCT00747305</td>
<td>28</td>
<td>Drabkin (USA)</td>
</tr>
<tr>
<td>A study of neoadjuvant Sutent® for patients with RCC</td>
<td>NCT00480935</td>
<td>30</td>
<td>Finelli (Canada)</td>
</tr>
<tr>
<td>Effect of sorafenib on RCC uptake of radiolabeled bevacizumab or cG250 prior to nephrectomy</td>
<td>NCT00602862</td>
<td>25</td>
<td>Mulders (The Netherlands)</td>
</tr>
</tbody>
</table>

3.3. Ongoing clinical trials on neoadjuvant targeted therapies

The potential for tumor downstaging or downsizing, improving the surgical field and reducing intra-operative and peri-operative morbidity are possible significant advantages of neoadjuvant targeted therapies for nonmetastatic RCC. The preliminary findings reported here support the exploration of a neoadjuvant therapy in clinical trials. At present neoadjuvant targeted therapies are possible only on experimental trials, and there are no guidelines or evidence for using them in clinical practice. Only on the basis of large, possibly phase III trials, a benefit of neoadjuvant targeted therapies can be calculated so as to include recommendations in the guidelines.

On the basis of the data presented here, neo-adjuvant trials should select patients: (1) with imperative indications for nephron-sparing surgery; (2) with high-volume RCC; and (3) with an extended vena cava thrombus. The outcome parameters to be investigated in these trials should be: (1) to facilitate surgery and to increase the possibility of removing the mass and (2) to improve oncological results in terms of risk of progression and survival.

Table 1 shows the ongoing trials. Because most of them have limited populations and have been developed as phase II trials, it is possible that the design of these studies and the results obtained at the end will not result in data that can be used for recommendations in international guidelines.

In particular, some open questions may be relevant when deciding on a neoadjuvant treatment. Currently, targeted therapies are recommended for RCC demonstrating a clear cell histology [8]. In metastatic RCC, data from the North American Advanced Renal Cell Carcinoma Sorafenib (N.Am-ARCCS) and European Advanced Renal Cell Carcinoma Sorafenib (EU-ARCCS) [38] expanded access programs confirmed the efficacy of sorafenib in patients with clear cell RCC. However, these treatments showed similar results for different histologies such as papillary, chromophobie or sarcomatoid (median PFS: 5.5 months in clear cell, 5.8 in papillary, 4.3 in sarcomatoid). Similar data are also available for temsirolimus [39] and sunitinib [40], which appear to be efficacious in patients with advanced non-clear cell RCC.

In the case of an indication for targeted therapies, only in RCC with clear cell histology is a biopsy on the primary tumor requested. However, in some cases, this point could be a limitation of the use of neoadjuvant therapies in nonmetastatic RCC. A second important question is the clinical evaluation of the time of maximal response to targeted therapy, so as to shift to nephrectomy. It is possible that the length of neoadjuvant therapy may be variable from one case to another. Currently, RECIST criteria are used as standard measures of treatment response, but these criteria are based on sizing parameters of the mass showing the tumor shrinkage determined by the therapy, they do not consider or measure tumor necrosis. Targeted therapies may lead to tumor necrosis rather than tumor shrinkage. Therefore, RECIST criteria cannot be the only criteria used to determine a neoadjuvant course of therapy, and new imaging modalities able to show and verify tumor necrosis are urgently needed.

3.4. Indications for adjuvant therapy

A question of particular relevance to the clinician is whether there is a role for targeted therapies as adjuvant treatment after nephrectomy. In the case of metastasis, targeted therapies are commonly used after surgery [41]. The question is whether, in the absence of metastasis, an RCC population suitable for adjuvant targeted therapy after nephrectomy can also be selected and identified.

Approximately 70% of patients with RCC have localized disease on diagnosis [13]. Therefore, the advantages of targeted therapy are currently offered only to a minority of patients with RCCs.

Nephrectomy can provide curative treatment for localized disease, but unfortunately 30% of patients will develop metastasis after surgery at a median time of 1.3 years [13]. This scenario seems to be ideal for adjuvant treatments.

Using an accurate post-operative stratification, patients at high risk of progression can be identified and offered adjuvant therapies.

The rationale for adjuvant treatment and its main characteristics are summarized in Table 2.

### 3.4.1. How to select patients after surgery

As already discussed, several prognostic models and nomograms have been developed to estimate the prognosis of patients with RCC, also for those at the nonmetastatic stage [20]. Models such as the UISS or the SSIGN system can be accurate after nephrectomy for predicting risk of progression or survival in nonmetastatic RCC. These two prognostic scores can select RCC patients who, despite the nonmetastatic stage, are at high risk of progression after surgery. Both of these have been extensively validated: the UISS with at least 8300 patients and the SSIGN with 2700 cases [13]. It is possible that in the coming years, scores integrating clinical with molecular (VEGF) parameters might give higher prognostic accuracy.

### 3.4.2. No proven previous adjuvant therapies

The adjuvant use of radiotherapy has been investigated and found to be equivalent to observation in terms of progression rate. However, it is also associated with significant morbidity and mortality (44% complication rate) [42]. Radiation therapy has been abandoned in the adjuvant setting.

Hormonal therapy with medroxyprogesterone acetate has also been explored, but no benefits have been found in terms of progression rate [43].

Data in the use of immunotherapy and cytokines as adjuvant to surgery are largely negative. Adjuvant IFN-α has been shown not to contribute to survival or progression [44]. A phase III trial on adjuvant IL-2 was closed early because disease-free survival was not affected and toxicity was significant [45]. Tumor vaccines have been also investigated.

The use of autologous irradiated tumor cells mixed with Bacillus Calmette-Guerin determined no significant disease-free survival benefits compared with observation [46].

A small advantage using adjuvant autologous tumor cell vaccine was obtained in Germany [47] with a five-year progression-free survival of 77.4% compared with 67.8% using observation.

Other vaccine strategies have been focused on the use of heat shock proteins such as VITESPEN, developed from autologous tumors in RCC. A multicenter phase III trial on adjuvant VITESPEN found no difference in progression-free survival compared with observation at a median of two years [48]. Another phase III trial has been recently concluded [23,49] on the adjuvant use of monoclonal antibodies (eG250-immunoglobulin G1 antibody) in metastatic RCC. They reported clinical benefit in 42% of patients and an overall survival of 30 months.

### 3.4.3. The ideal adjuvant therapy

In the choice of a specific targeted therapy as adjuvant treatment, the level of tolerability and a positive profile related to toxicity or side effects may play a relevant role. Sorafenib, sunitinib and temsirolimus represent effective treatment options for patients with metastatic RCC, but the drugs are not devoid of toxicity. The concept of toxicity should be relevant in the choice of the drug [49].

### 3.5. Ongoing phase III clinical trials on adjuvant targeted therapy

Currently, three major phase III clinical trials in the process of testing adjuvant targeted therapies in patients with RCC (Table 3).

The first is the Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC), which is designed to assess the effectiveness of one-year adjuvant sunitinib therapy (cycles of 50 mg/dl for four weeks followed by two weeks off-therapy) compared with placebo. The target patients are those with UISS high-risk RCC who have undergone nephrectomy. The primary end point of the study is disease-free survival. However, overall survival and safety will be considered as secondary end points. S-TRAC aims to recruit a limited pop-

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Investigator</th>
<th>Estimated accrual</th>
<th>Treatment arms</th>
<th>Primary outcome</th>
<th>Estimated end date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE SOURCE</td>
<td>National Cancer Institute</td>
<td>1332</td>
<td>Sunitinib versus sorafenib versus placebo Sunitinib 1 year versus sorafenib 3 years versus placebo</td>
<td>Disease-free survival</td>
<td>April 2016 August 2012</td>
</tr>
<tr>
<td>S-TRAC</td>
<td>Pfizer Inc.</td>
<td>290</td>
<td>Sunitinib versus placebo (1 year)</td>
<td>Disease-free survival</td>
<td>September 2011</td>
</tr>
</tbody>
</table>
ulation of 290 patients and the projected timeline for this investigation is July 2007–March 2011 [13,14,16,19–23].

More relevant results are awaited from the other two clinical trials: the ASSURE and the SORCE.

The Adjuvant Sorafenib, Sunitinib Unfavorable Renal Cell Carcinoma (ASSURE) trial is a multicenter double-blind randomized study analyzing 1923 patients who underwent nephrectomy for pT1b, G3–4; pT2–pT4; any T stage with node-positive disease. These patients will be stratified into an intermediate and high-risk group and than randomized to one year of oral sunitinib (50 mg/day for four weeks on-, two weeks off-therapy for a total of nine cycles), sorafenib (400 mg twice daily for six weeks for a total of nine cycles), or placebo. Treatments start between 4 and 12 weeks after surgery. This is a large Eastern Cooperative Oncology Group (ECOG) trial focusing on overall and disease-free survival. In addition, ASSURE will examine the effects of targeted therapies on non-clear cell RCC and differences related to the surgical technique (radical and partial nephrectomy, open versus laparoscopic surgery). It is also analyzing possible biomarkers (VEGF) and genetic mutations as predictors of therapeutic benefits. ASSURE started in May 2006 and the estimated date of completion is April 2016 [13].

The last study is the Sorafenib with placebo in patients with Resected Primary Renal Cell Carcinoma (SORCE) trial. It is a multicenter double-blind randomized study with an estimated enrolment of 1656 patients at risk of relapse after nephrectomy for RCC. Patients will be stratified on the basis of the Leibovich score at intermediate (scores 3–5) or high [6–11] risk. Eligibility for SORCE includes either clear cell or non-clear cell RCC at histology. All patients must have undergone surgery for RCC at least four weeks, but no more than three months, prior to study entry. Patients are randomized to three years of placebo versus one year of sorafenib, followed by two years of placebo versus three years of sorafenib. Sorafenib will be given at 400-mg bid doses.

The SORCE trial aims to answer two questions: the first is whether at least one year of treatment with sorafenib increases disease-free survival compared with placebo; the second, about the duration of adjuvant treatment, is whether three years of treatment increases disease-free survival compared with one year. The primary outcome is disease-free survival, but overall survival, toxicity and results related to RCC histology will be considered as well. The SORCE trial started recruitment in June 2007 and is estimated to be completed by August 2012 [13].

4. Conclusions

Surgery remains the standard care for nonmetastatic RCC. The introduction of targeted therapies and the significant results obtained at the metastatic stage have generated great interest in the possibility of expanding their application in the nonmetastatic RCC as well.

The rationale and need for neoadjuvant or adjuvant use of targeted therapies in RCC are relevant. The possibility of identifying high-risk patients and of offering treatment to those who would benefit from adjuvant or neoadjuvant therapy is realistic.

Case reports, phase II clinical trials on limited populations, reported encouraging results. However, to obtain recommendations from guidelines, larger studies are needed. Significant phase III trials on an adjuvant use of sorafenib and sunitinib in RCC are ongoing (ASSURE; SORCE) and clinicians are awaiting their final results in the hope that an adjuvant targeted therapy could be offered to extend disease-free survival.

Nevertheless, ongoing studies on the neoadjuvant use of targeted therapies remain limited and seem not to have the power for recommendations.

The hope is that the neoadjuvant and adjuvant approaches will represent a feasible new dimension in the treatment of nonmetastatic RCC.

Conflict of interest

None of the authors has any financial or personal relationships with organizations that could inappropriately influence the work.

Funding

None of the authors has a funding source for the work.

Reviewers

Camillo Porta, M.D., I.R.C.C.S. San Matteo University Hospital Foundation, Department of Medical Oncology, Piazzale C. Golgi, I-27100 Pavia, Italy.

Joaquim Bellmunt, M.D., Ph.D., Section Chief, Solid Tumor Oncology (GU and GI), Hospital del Mar, Medical Oncology Service, Passeig Marítimo 25–29, E-08003 Barcelona, Spain.

References


[34] Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm or less in a contemporary cohort. J Urol 2006;176(March (3)):730–6.


Biographies

Alessandro Sciarra, medical doctor, received his title of specialist in Urology in the School of Urology, University Sapienza of Rome, Italy. Now he is working in the Department of Urology “U. Bracci” of the University Sapienza of Rome and is responsible for a Prostate Unit there. He is currently a Professor in Medicine either for the School of Medicine or for the Schools of Urology and Nephrology at the University Sapienza of Rome. He has been member of the scientific committee of the Italian Society of Urology (SIU); referee for the European Association of Urology (EAU) and the European Urology Journal. His scientific activity has been published in the form of 104 contributions to various indexed international journals. Now he is also working in the Department of Urology “U. Bracci” of the University Sapienza of Rome. Current areas of research interest include urological oncology, mainly prostate cancer and kidney cancer, either as basic research or clinical studies.

Andrea Alfarone received his medical doctoral degree in 2005 from University Sapienza of Rome. He is currently working as a resident in urology in the School of Urology, University Sapienza of Rome, Italy. He is a member of several scientific societies (SIU, SIA, and EAU) and he is a leading expert on prostate cancer. His scientific activity has been published in the form of 15 contributions to various indexed international journals. Now he is also working in the Department of Urology “U. Bracci” of the University Sapienza of Rome. Current areas of research interest include urological oncology, mainly prostate cancer and kidney cancer, either as basic research or clinical studies.

Alessandro Gentilucci completed the urology residency at the School of Urology, University Sapienza of Rome, Italy, this year. He has been a member of the scientific committee of the Italian Society of Urology (SIU) and referee for the European Association of Urology (EAU) and European Urology Journal. His scientific activity has been published in the form of 18 contributions to various indexed international journals. He is currently working in the Department of Urology “U. Bracci” of the University Sapienza of Rome. Current areas of research interest include urological oncology, mainly prostate cancer and kidney cancer, either as basic research or clinical studies.

Ulderico Parente medical doctor resident in urology in the School of Urology, University Sapienza of Rome, Italy. He is a member of several scientific societies: the Italian Society of Urology (SIU), the Italian Society of Andrology (SIA), and the European Urology Association (EAU). He is currently working in the Department of Urology “U. Bracci” of the University Sapienza of Rome. Current areas of research interest include endourology and cancer, either as basic research or clinical studies.

Susanna Cattarino completed her medical schooling in 2009 at University Sapienza of Rome. She started the urological residency in the School of Urology, University Sapienza of Rome, in April 2010. She is a member of several scientific societies: the Italian Society of Urology (SIU), the Italian Society of Andrology (SIA), and the European Urology Association (EAU) and her scientific activity has been published in the form of 8 contributions to various indexed international journals. She is currently working as resident in the Department of Urology “U. Bracci” of the University Sapienza of Rome. Current areas of research interest include urological oncology, mainly prostate cancer and kidney cancer, either as basic research or clinical studies.

Gianna Mariotti medical doctor specialized in urology in the School of Urology, University Sapienza of Rome, Italy. Her research is focused on urological oncology, mainly prostate cancer and kidney cancer, either as basic research or clinical studies, and female urology. She has published several papers in Italian and English.
Michele Innocenzi received his medical doctoral degree in 2010 from University Sapienza of Rome. He is currently working as an M.D. at the Department of Urology “U. Bracci” of the University Sapienza of Rome. His main interest lies in urological oncology, mainly prostate cancer and kidney cancer.

Vincenzo Gentile medical doctor specialized in urology in the School of Urology, University Sapienza of Rome, Italy. He is currently working in the Department of Urology “U. Bracci” of the University Sapienza of Rome as Chief of the Department. He is Professor in Medicine either for the School of Medicine or for the Schools Urology and Endocrinology from the University Sapienza of Rome. He is President of the Italian Society of Andrology (SIA). His scientific activity has been published in the form of 110 contributions to various indexed international journals, most of them as first or last author. He has been primary investigator in different international trials, in particular on urological oncology and andrology. Current areas of research interest include urological oncology, mainly prostate cancer and kidney cancer, and andrology, either as basic research or clinical studies.