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Review – Renal cancer

Treatment of locally advanced renal tumors

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A B S T R A C T

Introduction: Locally advanced renal tumors show a high progression rate after surgery. Surgical treatment of renal tumors has some unique characteristics related to involvement of the adrenal gland, vena cava, or regional lymph nodes.
Objective: To review the current treatment of locally advanced renal tumors.
Materials and methods: A review is made of both the different drugs used and the different therapeutic possibilities in these tumors.
Results: Systemic treatment with angiogenesis inhibitors may improve the natural history of these patients. Systemic treatment may be administered before surgery or as an adjuvant to surgical treatment. Early studies showed a decrease in tumor mass when treatment is administered before surgery, but no prospective randomized studies providing adequate evidence for recommending neoadjuvant treatment are available.
Conclusions: Availability of systemic treatment with angiogenesis inhibitors may open an important field in the treatment of these tumors in both the neoadjuvant setting and as adjuvants to surgery, but no sufficiently solid scientific evidence as to recommend their use is currently available. Randomized studies with sunitinib and/or sorafenib will probably suggest the adequate approach to be used when their final results are reported.

Tratamiento de los tumores renales localmente avanzados

Palabras clave:
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Inhibidores de la tirosina quinasa
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Sorafenib
Tersirolimus
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R E S U M E N

Introducción: los tumores renales localmente avanzados presentan un alto porcentaje de progresión tras el tratamiento quirúrgico. El tratamiento quirúrgico de estos tumores renales presenta algunas peculiaridades en relación con la afectación de la glándula suprarrenal, de la vena cava o de la afectación de ganglios regionales.
Objetivo: revisar el tratamiento actual de los carcinomas renales localmente avanzados.
Material y métodos: se realiza una revisión de los distintos fármacos utilizados, así como de las distintas posibilidades terapéuticas en estos tumores.
Resultados: el tratamiento sistémico con inhibidores de la angiogénesis puede mejorar la historia natural de estos pacientes. La pauta de tratamiento sistémico puede ser preope-

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ratoria o adyuvante al tratamiento quirúrgico. Los primeros estudios realizados muestran una disminución de la masa tumoral cuando se realiza tratamiento preoperatorio, aunque no existen estudios prospectivos aleatorizados que nos den suficiente evidencia para recomendar la neoadyuvancia.

Conclusiones: la aparición de los tratamientos sistémicos con inhibidores de la angiogénesis puede abrir un campo importante en el tratamiento de estos tumores, tanto en neoadyuvancia como en adyuvancia a la cirugía, pero en la actualidad no tenemos evidencias científicas suficientemente sólidas para recomendar su uso de forma indiscriminada. Probablemente serán los estudios aleatorizados con sunitinib y/o sorafenib los que marcarán la pauta a seguir cuando se completen los resultados definitivos.

Introduction

The treatment of choice for locally advanced renal tumors and other non-metastatic renal tumors continues to be surgery[1]. The rate of progression after radical nephrectomy is between 30 and 88%[2,3], which is significantly higher than for localized tumors[2]. This high rate of progression, and the experience of improved survival when systemic therapies are added to the treatment of other kinds of cancer (e.g., colon) has led to attempting to improve the outcomes of surgery for this type of renal cancer. The biologic characteristics that render renal cell carcinoma resistant to radio- and chemotherapy have oriented the strategies towards immunotherapy in association with surgery. None of the immunotherapy regimens used (alpha-interferon, interleukin 2) or their status as adjuvant or neoadjuvant treatments have been shown to improve the survival of patients with locally advanced renal cell carcinoma[4,5]. In the past few years, a strategy has been developed that has proved effective for treating metastatic renal cell carcinoma: angiogenesis inhibition. There are several families of angiogenesis inhibitors, including tyrosine kinase inhibitors (sunitinib, sorafenib), mTOR blockers (temsirolimus), and monoclonal antibodies (bevacizumab)[6]. The poor response to immunotherapy and the outcomes with angiogenesis inhibitors in metastatic renal cell carcinoma have reignited interest in systemic treatments for the purpose of improving the survival of patients with this disease. This article reviews the best current therapeutic options for this type of renal tumor.

Material and methods

A PubMed bibliographic search for several items was conducted. In all cases, the search started in the MeSH database for MEDLINE/PubMed using "Carcinoma, Renal Cell" as the main heading, and "Therapy" as the subheading. The terms "locally advanced" was added in the PubMed search. For surgical treatments, reviews referring to locally advanced renal cell carcinoma were used, and reviews of local tumors and metastatic tumors were discarded. For the analysis of systemic treatment, randomized clinical trials and case series were included in addition to reviews. Additionally, the same search criteria were used in the NCBI Clinical Trials database with the purpose of assessing ongoing clinical trials with yet unpublished outcomes.

Definition of locally advanced renal cell carcinoma

The UICC TNM classification of 2002 classifies renal cell carcinomas as pT3 when the tumor involves the venous system (pT3b-c), the adrenal gland, or the perinephric tissue (pT3a) if it does not extend beyond the Gerota fascia (renal fascia), and as T4 if the tumor goes beyond the Gerota fascia. N1 means that there is one lymph node involved, and N2 means that there is more than one lymph node involved. This classification has been criticized by several institutions because it does not reflect homogeneous prognostic groups.

The most controversial is subgroup pT3a because adrenal gland invasion has a worse prognosis than perinephric fat and renal sinus involvement[7], the prognosis for the latter being similar to that of localized tumors (pT1/pT2) if the tumor is small (less than 5.5 cm)[8].

Based on the heterogeneity of pT3a patients (adrenal gland, perinephric fat and renal sinus invasion) and on the different prognostic value when the tumor thrombus involves the renal vein or the infradiaphragmatic vena cava (both pT3b), a European study[3] has proposed replacing the current classification with three prognostic groups according to the type of local extension of the tumor.

It has been established that pT3 tumors in patients with vascular involvement have a higher percentage of recurrence, but this is not associated with a lower survival rate[9-11].

Surgical treatment

Radical nephrectomy is the first choice treatment for locally advanced renal tumors. The procedure consists of removing

en bloc the kidney with the perinephric fat, the adrenal gland, and the Gerota fascia. Approaches vary according to the location and size of the tumor, the patient's characteristics, and even the surgeon's preferences[12]. The main approaches currently are transperitoneal (anterior), retroperitoneal (lumbotomy), thoracoabdominal, and laparoscopic.

Locally advanced tumors may present some unique characteristics that allow for (or require) a modification of the surgical technique.

Adrenalectomy

Although the definition of radical nephrectomy includes the removal of the adrenal gland, given the increased sensitivity and specificity of imaging techniques and the low percentage of adrenal invasion in the surgical pieces, for some years now the adrenal gland has been preserved after nephrectomy. Furthermore, even when adrenal involvement is observed in preoperative tests, approximately 50% of adrenal pathology may be benign, not due to tumor invasion[13]. In her review (May 2009), O'Malley concludes that the standard practice of adrenalectomy in patients with tests not suggestive of tumor invasion is not recommended, and that adrenalectomy should be reserved for patients whose imaging suggests invasion or who have risk factors such as mutifocality, tumor larger than 7 cm, upper pole location, or vascular involvement (T3b-c)[14].

Vascular involvement

The surgical approach in patients with tumor thrombus depends of the level of the thrombus[15]. Renal vein and infrahepatic vena cava involvement do not have a significant effect on the surgical approach of radical nephrectomy, but a greater dissection and clamping of the vena cava are usually required. When in addition to tumor thrombus there is invasion of the wall of the vena cava, resection of the affected area is necessary, as is the reconstruction of the defect with direct suturing (with resections under 50% of the vein's circumference) or by placing patches of various materials[16] such as autologous vein, pericardium, or synthetic patches.

Intra- and suprahepatic vena cava involvement requires complete liver mobilization; the surgical field may be more amply exposed if a xyphoid incision is used. Vascular bypass has been proposed for some cases, as it reduces the operative time, the hospital stay, and perioperative complications, compared to the traditional cardiopulmonary bypass[17].

Although currently right atrium tumor thrombi are uncommon because kidney masses are diagnosed earlier, the diagnosis of this type of patient represents a therapeutic challenge that requires a thoracoabdominal approach and in most cases extracorporeal circulation. The extracorporeal circulation technique used should be a cardiopulmonary bypass with cardiac arrest and deep hypothermia[18]. This surgery has a high morbidity and mortality[19] and should be performed only in hospitals with ample experience in heart surgery.

Lymphadenectomy

Radical nephrectomy often entails removing lymph nodes around the renal hilus. According to Robson's description[20], radical nephrectomy includes paraarotic and paracaval lymphadenectomy, and positive nodes are found in 27% of patients. Today, after the studies conducted by EORTC[21] and the Mayo Clinic[22], a significant decrease in node involvement has been observed when lymphadenectomy is done at the time of the radical nephrectomy (tumor infiltration of the dissected nodes is seen in 3-4% of patients). Furthermore, in patients in whom lymph node involvement is not suspected preoperatively, lymphadenectomy does not improve survival compared to radical nephrectomy only[23,24]. These data suggest that routine lymphadenectomy is not required with radical nephrectomy in patients without preoperative suspicion of node involvement. However, in patients in whom imaging techniques suggest tumor invasion of regional lymph nodes, aggressive retroperitoneal lymphadenectomy may prolong survival if there are no remote metastases[25], so lymphadenectomy is indicated in these patients.

Adjacent organ involvement

Liver, duodenum or pancreas local invasion by renal cancer is uncommon. Large tumors tend to compress adjacent structures, but the tumor capsule limits and delays contiguous invasion. In addition to abdominal viscera, renal tumors can also invade the lumbar or paraspinal muscles or the nerve roots; in such cases, patients experience important lumbar or neuralgic pain. When local invasion is confirmed, the organs are removed en bloc, but prognosis is very poor in all cases, with a survival rate of less than 5% at 5 years after treatment.

Systemic treatment

The development of angiogenesis inhibitors and the evidence of increased survival in patients with metastatic tumors treated with these therapies vs. immunotherapy has opened several options of systemic treatment for renal cancer which immunotherapy had not offered. In patients with locally advanced renal tumors, surgery may reduce the rate of recurrence and/or progression. Several adjuvant treatments to reduce the rate of progression of locally advanced tumors have been assessed, such as radiation, hormone, and immunotherapy (alone or combined with chemotherapy). None of these treatments has shown to improve survival in these patients. One prospective, phase III study compared post-nephrectomy treatment with renal tumor cell vaccines vs. observation, and showed better survival in patients who were treated compared to those who were not (77.4% vs. 67.8%); this difference is statistically significant[26]. The objections to this study are the large number of patients lost after randomization (32%, with a higher loss among treated patients), and the lack of data on overall survival.

The study of angiogenesis inhibitors stems from a better analysis of the biological behavior of renal cell carcinoma. Up to 75% of non-hereditary clear cell carcinomas present Von Hippel Lindau (VHL) suppressor gene mutations[27]. This results in increased hypoxia-inducible factor 1 (HIF-1), which stimulates the generation of growth factors such as the vascular endothelial growth factor (VEGF) (VEGF) and the platelet-derived growth factor (PDGF). These growth factors have a paracrine action via tyrosine kinase receptors. The result is an increase in angiogenesis and cell growth and survival. This explains the anti-angiogenesis action of tyrosine kinase inhibitors such as sorafenib and sunitinib, and of the monoclonal antibody that blocks VEGF (bevacizumab), which inhibits the action of this growth factor. The mTOR pathway (which is blocked by temsirolimus) is not tyrosine kinase-dependent. Activation of the mTOR pathway causes increased expression of HIF1 and proangiogenic cytokines.

Tyrosine kinase inhibitors

Sunitinib

Sunitinib inhibits the receptor tyrosine kinases VEGFR1-2, PDGFR, FLT-3 (FDGFR-like receptor), and the C-kit receptor. The therapeutic dose is 50 mg/day for 4 weeks, with two weeks off between cycles. The most common side effects are fatigue, diarrhea, and nausea[5] (Table 1).

Several phase I studies showed the antiangiogenic and antitumor effects of this product on metastatic renal cell carcinoma and other tumors; dosage is limited by toxicity. Two phase II studies with 169 patients demonstrated its efficacy as second-line therapy in patients with metastatic renal tumors[28,29], with a 34% partial response and a mean progression-free survival of 8.3 months.

The indication as first-line therapy for metastatic tumors arose after a phase III study comparing sunitinib 50 mg for 4 weeks every 6 weeks vs. alpha-interferon (INF-α) 9 million units subcutaneously three times per week. This study showed a progression-free survival of 47.3 weeks with sunitinib therapy vs. 24.9 weeks for INF-α treatment[30].

There are two ongoing studies comparing the efficacy of 37.5 mg/day vs. the currently used 50-mg regimens to assess the persistence of efficacy with possible decrease in side effects.

Sorafenib

Sorafenib is a multi-kinase inhibitor that blocks several receptors, such as C-RAF, B-RAF, VEGFR2-3, PDGFR, Flt 3, and C-kit. The therapeutic dose used is 400 mg twice a day.

The most important side effects are diarrhea, skin reaction, asthenia, and hand-foot syndrome (Table 1).

One phase II study compared the progression of metastases in patients with renal cell carcinoma treated with sorafenib vs. those treated with placebo; at 24 weeks there was stabilization of the metastatic lesions in 50% of patients treated with sorafenib vs. 18% among those treated with placebo[31]. A phase III trial studied patients with metastatic renal cancer randomized to sorafenib 400 mg twice daily continuously or placebo after initial systemic therapy; the progression-free survival was 84 days for those treated with placebo, and 167 days for those on sorafenib. Moreover, the percentage of patients with some type of progression (clinical, radiologic, or death) was significantly higher among subjects receiving placebo than among those treated with sorafenib (50% vs. 38.3%)[32].

Temsirolimus

The m-TOR pathway acts as a complex autocrine and paracrine regulation system that coordinates cell growth and the progression along the cell cycle by regulating the availability of nutrients, energy, and growth factors.

Table 1 – Main side effects of angiogenesis inhibitors

	Sunitinib	Sorafenib	Temsirolimus	Bevacizumab
Fatigue	X	X	X	
Diarrhea	X	X	X	
Nausea	X	X	X	
Skin reaction		X		
Hand-foot syndrome		X		
Anorexia	X		X	
Dyspnea			X	
HT				X
Proteinuria				X
Skin rash			X	X

HT: hypertension.

Temsirolimus blocks the m-TOR pathway, preventing the phosphorylation of various cell molecules and thus inhibiting RNAm translation, which blocks the cell cycle at the G1 phase. The most important side effects are fatigue, anorexia, dyspnea, and diarrhea (Table 1).

In patients with poor prognosis, temsirolimus has increased overall survival (10.9 months) compared to INF-α therapy (7.3 months), and has lower toxicity[33].

Bevacizumab

Bevacizumab is a monoclonal antibody against VEGF and produces a decrease in angiogenesis. The most common side effects observed with this treatment are high blood pressure and asymptomatic proteinuria (Table 1).

In patients with metastases after systemic therapy, monotherapy with bevacizumab increased the median of progression-free survival compared to placebo (4.8 months vs. 2.5 months)[34]. The first phase III study of renal cancer with this angiogenesis inhibitor was done by adding bevacizumab to INF-α therapy, and comparing this to INF-α plus placebo. Bevacizumab therapy had a response of 31.4% vs. 12.8% for placebo; furthermore, the mean progression-free survival was 10.2 months for the bevacizumab group vs. 5.4 months for the placebo group.

Neoadjuvant therapy

In theory, in patients with locally advanced renal tumors, the association of surgery with systemic therapy may improve the course of the disease. While it is understood that the definitive treatment is surgery, many patients present with primary tumors that are potentially unresectable due to their size, renal hilus invasion, large lymphadenopathies, major vascular involvement, or invasion of adjoining structures. Neoadjuvant therapy with angiogenesis inhibitors, which has demonstrated to be effective in metastatic tumors, can shrink the tumor and thus facilitate surgical resection, and therefore survival. There are no randomized studies with enough evidence to recommend neoadjuvant therapy in these patients; however, there are small series in which a tumor size reduction, downstaging, and even a decrease in the size of the vascular tumor thrombus were observed[35-38]. In most cases sorafenib or sunitinib were used in association with bevacizumab or even INF-α in some patients. In no case was systemic therapy capable of achieving a complete response with disappearance of the tumor. There are several studies in the recruiting stage sponsored mainly by the United States National Cancer Institute that assess the safety of neoadjuvant therapies and the molecular and pathological changes induced after nephrectomy. A study conducted by the *Sociedad Española de Oncología Médica*, which is currently recruiting patients, will assess the efficacy of neoadjuvant therapy with sunitinib in terms of progression-free survival and overall survival. The Cleveland Clinic is conducting a phase II open study with neoadjuvant therapy in which patients with tumors larger than 15 cm, lymphadenopathies larger than 4 cm, in stage T3c or with involvement of vital structures, initiate treatment with sunitinib 50 mg/day for 4 weeks. If the disease progresses, an alternative systemic therapy is initiated; if there is response to sunitinib, a nephrectomy is performed[39]. These studies will not be completed until 2010, and the results will inform us about treatment with angiogenesis inhibitors as neoadjuvant therapy with nephrectomy for this kind of cancer.

Adjuvant therapy

About 30% of "disease-free patients" after nephrectomy present with metastasis during follow-up for renal cancer[2]. This percentage increases if there is extracapsular, venous or nodal involvement[40,41]. Adjuvant therapy for patients with a high risk of progression may act on the tumor cells present after surgery that are responsible for the development of metastases, and thus improve survival in these patients. None of the agents studied to date (radiation, hormone or immunotherapy) have been capable of confirming the above statement[4,5,42,43]. The challenge of angiogenesis inhibitors is to modify the natural course of renal cell carcinoma in this group of patients with a high risk of progression. The first randomized study comparing thalidomide (immunomodulating and antiangiogenic effect) to observation of locally advanced renal cell carcinoma treated with radical nephrectomy has not shown that thalidomide improves progression-free survival or cancer-specific mortality[44].

Currently there are three large multicenter randomized phase III studies which will probably provide sufficient evidence to add or discard adjuvant therapy to nephrectomy. The SORCE (Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer) study includes patients at intermediate and high risk of progression (Leibovich score) after radical nephrectomy without evidence of residual tumor, who are divided into three treatment arms: a) placebo; b) sorafenib (40 mg twice daily) for one year, and afterwards, placebo until three years are completed; and c) sorafenib (40 mg twice daily) for three years. The main objective is to assess progression-free survival. The secondary objectives are to measure overall survival, disease-specific survival, metastasis-free survival, and cost-effectiveness and toxicity. The study intends to enroll 1656 patients by August 2012, and definitive results will not be available until at least 2013[45]. The ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) study will enroll 1923 patients at intermediate or high risk of recurrence after radical nephrectomy with no evidence of residual tumor, who will be randomized in three treatment arms: a) placebo; b) sunitinib (50 mg/day); and c) sorafenib (400 mg/12 hours). The primary objective is also to compare the progression-free survival of patients in the three groups; data are expected to be collected in 2016[46]. The third phase III study is the S-TRAC (Sunitinib Treatment of Renal Adjuvant Cancer). It includes patients a high risk of recurrence according to UISS (UCLA Integrated Staging System) criteria. The study will randomize 256 patients in two treatment arms: one with placebo and the other with

sunitinib 50 mg/day. Like the other studies mentioned, its primary objective is to compare disease-free survival in the two study groups[47]. Data collection is expected to be complete in 2016.

The final results of these three randomized studies will provide important information about adjuvant therapy.

Conclusions

Treatment of locally advanced renal tumors continues to be surgical. Availability of systemic therapies with angiogenesis inhibitors may open an important field in the treatment of these tumors in both the neoadjuvant setting and as adjuvants to surgery; however no sufficiently solid scientific evidence as to recommend their use is currently available; these therapies are indicated only within the context of clinical trials. The final results of the ongoing studies will determine whether these therapies improve patient survival, and if so, what group of patients will benefit from this.

Conflict of interest

The authors state that they have no conflicts of interest.

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