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Adjuvant and Neoadjuvant Therapy in Renal Cell Carcinoma

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Abstract

Nephrectomy continues to be the cornerstone of treatment for localized renal cell carcinoma (RCC). Despite undergoing nephrectomy, recurrence of disease remains a concern in many patients, and different medical therapies are being investigated as means to decrease this risk. The use of the traditional immunotherapy options has not provided benefit as adjuvant treatment in this disease state. Recently, the treatment of metastatic RCC has experienced key advances with the introduction of targeted agents against the vascular endothelial growth factor (VEGF) molecule and related pathways as well as inhibitors of the mammalian target of rapamycin (mTOR), in addition to improvements in surgical technique. Additionally, there are questions about the optimal timing of systemic therapy in the context of high risk non-metastatic disease. There is optimism that locally advanced RCC might benefit from adjuvant or neoadjuvant treatment with these therapies. Ongoing clinical trials are addressing the role of targeted agents in this disease state.

Introduction

Tumors of the kidney and renal pelvis will affect over 58,000 individuals in the USA in 2011, and will result in around 13,000 deaths in that country [1]. It is estimated there will be over 100,000 deaths due to renal cell carcinoma (RCC) worldwide [2].

More than 75% of patients diagnosed with RCC present with either localized or locally advanced disease [3]. For these patients, surgical resection of the primary tumor is performed with curative intent. Unfortunately, many patients relapse, either locally at the site of nephrectomy or most commonly at distant sites [4]. Once metastatic, prognosis from RCC is poor, and the large majority of patients will die of their disease [5]. The risk of recurrence depends on factors related to the tumor biological features such as pathologic stage, Fuhrman nuclear grade as well as the patient's overall health status as defined by the Eastern Cooperative Oncology Group Performance Status (ECOG PS) [6-8]. It ensues that identifying patients at high risk for relapse through well-validated prognostic models is important for tailoring surveillance and treatment plans. or these patients, it appears intuitive that adjuvant therapy options would be required to treat microscopic disease. Such a treatment however should ideally be easily administrable, devoid of major adverse effects, and efficacious against metastatic disease.

The task of developing adequate adjuvant therapies has been thwarted by the radio-resistant and chemoresistant nature of RCC. Multiple post-operative adjuvant modalities have been evaluated such as radiotherapy [9], immunotherapy with cytokines [10,11] or medroxyprogesterone acetate [12], and vaccination with patient-derived tumor antigens [13], without improvement in disease free survival (DFS) or overall survival (OS).

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With the recent advent of the targeted therapies, an improvement in progression free survival (PFS) has been shown [14-17] in the setting of metastatic RCC (mRCC), with shrinkage in size of both the primary tumor size and the metastatic sites, unlike the traditionally used immunotherapy regimens [18,19]. The availability of agents active against metastatic disease raises the hope that these agents can be also used as an effective adjuvant treatment and possibly as a neoadjuvant option. We aim to review the literature pertaining to this topic.

Materials and methods

Data for this review were obtained through a Medline/PUBMED search for articles in the English language using the keywords renal cell carcinoma, adjuvant treatment, neoadjuvant treatment, tyrosine kinase inhibitors (TKIs), and nephrectomy.

Prognostic models in RCC

The identification of patients at high risk for relapse and of patients who are likely to respond to treatment is essential to design directed treatment and postoperative surveillance plans. Patients at high risk of recurrence will likely require more aggressive follow-up and will be candidates for enrollment in clinical trials for adjuvant treatment. The prediction of which patients respond to specific treatments will allow for adapted treatment options, while also avoiding the adverse effects of non-effective treatments. For that purpose, several prognostic models have been designed to predict the risk of recurrence and 5 year OS in both the metastatic and non-metastatic disease settings.

The University of California at Los Angeles (UCLA) integrated scoring system (UISS) is a commonly used nomogram to predict the risk of relapse or survival post nephrectomy in patients with localized RCC. The UISS model developed at the UCLA in 2001, and modified in 2002, comprises the 1997 tumor node metastasis stage (TNM), Fuhrman grade, and Eastern Cooperative Oncology Group performance status (ECOG PS) to classify patients into low, intermediate or high risk groups [6,20]. Patients with local disease in the low risk group have an 84% 5-year OS compared to 44 % in the high risk group. This score was validated in an international multicenter trial in 2004[21].

The Mayo Clinic stage, size, grade, and necrosis (SSIGN) [22] and the Leibovich model [8] are similar models used to predict cancer free survival and metastasis free survival respectively. They are based on the (TNM) system, tumor size, grade of differentiation, and both include histological necrosis as a criterion [22].

Other prognostic models rely on clinical variables only to identify high risk patients, such as the models proposed by Yaycioglu [23] and Cindolo [23,24]. Clinical models are beneficial in circumstances where the complete pathological staging is not readily available, as in the example of tissue obtained through minimally invasive approaches are performed.

The above-mentioned models are based on clinical and pathological data, but do not include molecular data. As our understanding of the RCC tumor biology evolves, new molecular markers will be identified, and may account for some of the observed disease heterogeneity. These markers may help further stratify RCC into molecularly and clinically defined prognostic subgroups, and may provide predictive information, leading to the development of more tailored treatment plans.

Potential prognostic biomarkers include von Hippel Lindau (VHL) tumor suppressor gene mutations [25], elevated levels of vascular endothelial growth factor (VEGF) [26], Ki-67[27], matrix metalloproteinases 2 and 9 [28] and possibly p53 overexpression [29].

Results from other protein analyses like carbonic anhydrase 9, which is highly expressed in clear cell RCC have been less conclusive [30,31].

When combined with clinical data, these molecular marker signatures may improve disease free survival (DFS) prediction accuracy. A molecular model published by Klatte et al was based on the immunohistochemical analysis of tissue microarrays of the primary tumors from 170 patients. Five molecular markers (Ki-67, p53, endothelial VEGFR-1, epithelial VEGFR-1, and epithelial VEGF-D) were found to be independent predictors of DFS. When a nomogram combining the five markers with the TNM stage and ECOG PS was tested, a concordance index of 0.904 was reached [32]. These types of prognostic tools, although promising, require independent validation and standardization of immunohistochemical techniques to gain wider usage.

Role of nephrectomy in nonmetastatic disease

Nephrectomy remains a keystone in the treatment of localized RCC. First introduced in 1963 by Robson [33], open radical nephrectomy (ORN) resulted in a 5 year overall survival (OS) of 66 % [34] and became standard of care for localized disease. Newer techniques have emerged over the last two decades, such as the laparoscopic radical nephrectomy (LRN) and nephron sparing surgical (NSS) resection. These techniques have resulted in 5 year OS survival rates similar to ORN [34-36] with the LRN also resulting in the expected outcomes of less perioperative complications and better cosmesis.

NSS aims at resection of the tumor [37], while preserving unaffected renal function [38,39]. This technique, which has become popular in specialized centers [40] as opposed to the community based urological practices [41], is favored for stage T1a of the disease (tumor size <4cm) although larger tumors have also been removed [42,43]. It also prevents the loss of complete renal function, a factor that has been associated with a shorter OS [44]. Partial nephrectomies have also resulted in the restriction of adrenalectomy and lymphadenectomy to patients with disease stage of large tumors (> 7 cm) or radiologic evidence of adrenal involvement or lymphadenopathy [45,46]. However, NSS is still underutilized and ORN remains the most commonly performed approach [47].

Adjuvant therapy with immunotherapy

Progression of RCC tends to occur most commonly at sites distant from the primary tumor. Because of this, effective adjuvant therapy needs to target the circulating tumor cells, and nascent micrometastatic sites. Timing of the adjuvant treatment administration may also be important, and it appears intuitive to treat patients when the tumor burden is the most depleted after surgical resection.

A number of therapeutic approaches have been tested in RCC. Because patients with RCC mount an immune response against tumor cells antigens located on the cell surface, immunotherapeutic agents have been developed and tested. This immune response, initiated by CD8+ cytotoxic T lymphocytes, is amplified through the secretion of cytokines such as IL-2 and IFN-α by CD4+ helper cells [48]. This served as the basis of testing these two cytokines as an adjuvant treatment, when the immunosuppression by the renal tumor has ceased [48]. Other modalities of immunotherapy such as autologous tumor cell vaccination and hormonal therapies have also been attempted (Table 1).

Studies published in the 1990s indicated that IFN-α [49]and the combination IFN-α and vinblastine[50] were shown to improve survival in patients with metastatic RCC and high-dose IL-2 showed a 5 % complete response rate[51], raising the hope that these therapies can be used as an adjuvant treatment for localized disease. Many retrospective and prospective studies have been conducted to determine the effectiveness of these two drugs in

the adjuvant setting but none showed improvements in DFS or OS when compared to observation. [52-55] In a clinical trial conducted by Clark et al in 2001 [11] evaluating the role of adjuvant IL-2 in locally advanced RCC, 16 of 21 patients relapsed in the treatment arm compared with 15 of 23 patients in the observation arm (p=0.79). Similar results were obtained with two trials involving IFN- α [10,56], the most recent of which was conducted by Messing et al in 2003. Adjuvant treatment with IFN-α in patients with pT3-4a and/or node-positive disease resulted in a median survival was of 7.3 years in the observation arm compared with 5.1 year in the treatment arm (P =.09), with 11.4 % of the patients experiencing severe toxicities. Comparable outcomes were observed when the combination of IFN-α, IL-2 and 5-fluorouracil was compared to observation alone [57].

Another approach to immunotherapy consists of patient-derived vaccines [58]. No clear benefit has been shown so far [13], although one study hinted at a possible improvement in PFS [59], but a critique of the study was that many patients in the vaccine arm never received the vaccine. A more recent 728 patient clinical trial investigated the use of vitespen, an autologous, tumorderived heat-shock protein 96 as an adjuvant treatment and showed no difference in recurrence-free survival [60], with a 37% and 40% recurrence rate in the treatment and observation arms respectively.

The reason for the failure of multiple immunotherapy options is not clear, and new potent immunomodulatory molecules, including cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death -1 (PD1) inhibiting agents have been developed to more precisely modulate T-cell biology. Anti CTLA-4 therapy has shown promise in the setting of metastatic melanoma, another immunogenic tumor. The hope is that these agents may improve outcome in patients with high risk RCC. [61]

Adjuvant treatment with targeted therapies

In 2005, sorafenib was the first anti-VEGF agent to show improved PFS compared to placebo in metastatic second line RCC [62]. Similar results were reported with pazopanib [63], sunitinib [14], and the combination of bevacizumab and IFN-α [16,17]. For patients with poor prognostic features as defined by a modified MSKCC algorithm, temsirolimus, an mTOR inhibitor showed a prolonged OS when compared to interferon monotherapy and the combination of both drugs [64]. With this improvement in PFS and OS, targeted therapies have replaced immunotherapies in the metastatic setting.

The promising results with inhibition targeted agents in metastatic RCC has spurred their evaluation in the adjuvant therapy setting These agents may inhibit the development of neovasculature in nascent metastases through inhibition of the VEGF receptor function with oral small molecule TKIs (sunitinib, pazopanib, sorafenib) or with a monoclonal antibody against circulating VEGF molecules, bevacizumab. In RCC, VEGF is an important downstream factor in a cascade that starts with mutated VHL. This gene regulates hypoxia induced factor 1 and 2 alpha (HIF 1-α and HIF 2-α), two transcription factors involved in the expression of multiple proangiogenic factors including VEGF. The inhibition of VEGF diminishes some of the downstream changes initiated by mutated VHL and hence alters the angiogenic signal necessary for the growth of tumors beyond a relatively small size.

Molecularly targeted agents regimens are currently being investigated as monotherapy. However, combination therapies might be needed to target different aspects of the metastatic process, which involves sequential steps [65] including invasion, intravasation, survival in the peripheral circulation, extravasation in the new organ parenchyma, and finally proliferation and angiogenesis. A deeper understanding of the mechanism of metastatic progression in RCC will permit the application of more appropriate agents for specific patient and tumor phenotypes.

Five randomized, double-blind clinical trials are currently underway to test the role of the currently available molecularly targeted agents, and are either recruiting or have completed recruiting patients. Four trials are investigating the role of sorafenib, sunitinib and pazopanib as adjuvant therapies in RCC. These trials include the Adjuvant Sorafenib or Sunitinib in Unfavorable Renal Cell Carcinoma (ASSURE) (NCT00326898) [66]. Sorafenib with Placebo in Patients with Resected Primary Renal Cell Carcinoma (SORCE) (NCT00492258) [67], the Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) (NCT00375674) [68], and the Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma (PROTECT) (NCT01235962) trials [69]. Another trial, the EVerolimus for Renal Cancer Ensuing Surgical Therapy (EVEREST) will investigate the role of everolimus as an adjuvant agent [70].

The ASSURE trial is led by the ECOG Initiated in 2006, it recruited over 1900 patients with non-metastatic disease. The trial has three arms comparing sunitinib with placebo, sorafenib with placebo and sunitinib with sorafenib head to head. This trial enrolled patients with non-clear cell RCC and hence will help extend our understanding of this population. In addition, this trial will study markers that could predict the likelihood of relapse or of benefit, and aims at comparing the outcome of patients who undergo open versus laparoscopic nephrectomies. Finally, the authors will study whether the toxicity profile of the agents used can be predicted by the analysis of cyt p3A4/5 polymorphisms.

The second trial investigating the role of sorafenib as an adjuvant therapy is the SORCE trial. Initiated in 2007, it is a three-arm study aiming at recruiting 1656 patients at high or intermediate risk of relapse (Leibovich score 3–11), who have undergone nephrectomy and are systemic treatment naïve. It will compare 3 years of treatment sorafenib with 1 year of treatment with sorafenib plus 2 years of placebo versus placebo for 3 years. This trial is expected to complete accrual in 2012 and will include patients with both clear cell and non-clear cell carcinomas.

The S-TRAC trial will compare treatment with sunitinib for one year versus placebo in patients at high risk for recurrence. The estimated enrollment of 600 patients is expected to be completed in December 2011. This trial will include patients with predominant clear cell histology with no evidence of macroscopic disease after nephrectomy. Patients in the treatment arm will receive oral sunitinib malate 50 mg on a schedule consisting of 4 weeks on, 2 weeks off for 1 year or until disease recurrence or development of severe side effects.

The fourth trial investigating will compare pazopanib to placebo. Sponsored by GlaxoSmithKline, it has an expected enrollment of 1500 patients with clear-cell or predominant clear-cell histology and non-metastatic disease who have undergone a nephrectomy. Launched in November 2011, it is expected to complete accrual in October 2015. Patients in the experimental arm will receive 800 mg of pazopanib daily for one year.

The primary endpoint in these four trials is disease free survival with secondary endpoints including OS, drug safety and patient-reported outcomes. The ASSURE and SORCE trials will also examine blood and tissue samples to study possible indicators of benefit from the drugs administered.

Another phase 3 clinical trial due to start recruitment soon is the EVEREST trial. Sponsored by the SWOG and the NCI, it aims at comparing the recurrence-free survival of patients with RCC treated with everolimus versus placebo after nephrectomy or partial nephrectomy. The accrual is expected to end in February 2013 with an expected enrollment of 1218 patients. Patients in the experimental arm will receive nine courses of six weeks of daily oral everolimus in the absence of disease progression or significant adverse effects. The

secondary endpoints will be OS and the collection of tissue to test for molecular biomarkers related to the AKT/mTOR and other pathways involved in RCC.

Neoadjuvant treatment

The role of neoadjuvant treatment for localized RCC is even less clear than adjuvant treatment, and the available data is obtained primarily from studies on cytoreductive nephrectomy in the presurgical setting.

TKIs can possibly downsize the primary RCC tumor. In a study on 17 patients with mRCC, sunitinib induced a 31 % shrinkage in tumor size [71]. For localized RCC, neoadjuvant treatment would be beneficial to downsize or downstage primary tumors that are considered unresectable, such as tumors associated with vascular invasion, bulky regional lymphadenopathy, or proximity to vital organs[72]. Neoadjuvant therapy could be also considered for tumors originating from a solitary kidney, or to reduce and normalize the tumor vasculature [73,74], as well as selecting the responders who will benefit the most from surgery[75].

But unresectability is a subjective term, and depends largely on the level of expertise available at the treatment facilities, and experience with the procedures. In fact, rates of pure non-resectability have been reported to be less than 1% in some institutions [82]. Whether downsizing of the tumor has any bearing on the oncological clearance of the disease or a role in simplifying surgical resection is unclear. In one study, primary tumors shrank on average 9.5% with targeted therapies [80]. A slight decrease of this magnitude in the size of the primary tumor is unlikely to be of clinical relevance. In addition, the role of neoadjuvant treatment in simplifying the surgical resection and making the tumor amenable to an elective nephron-sparing surgery is also questionable [83]. However, patients who have involvement of the IVC (T3b or T3c) will probably benefit more from targeted therapies as the decrease in the tumor volume facilitates the surgical procedure [84]. Ideally, neoadjuvant therapy should decrease tumor size, but also truly downstage disease. This would be manifested by regression of inferior vena caval thrombi, regression of tumor from extracapsular regions, and decrease in size that would permit the conversion of an operation from a complete to a partial nephrectomy. Whether the current generation of agents is capable of achieving these goals is unclear, and future trials need to carefully define the endpoints associated with clinical benefit.

The safety of targeted therapies in the perioperative period is under debate. Targeted therapy agents might interfere with wound healing. [76-78]. In view of the potential for perioperative complications, Bevacizumab, which has a half-life of 20 days is usually stopped six weeks prior to surgery, whereas the TKIs that have a shorter half-life, and may require a shorter wash-out period prior to surgery. A retrospective study at the university of Texas at MD Anderson Cancer Center (MDACC) compared patients who had received neoadjuvant treatment with either sunitinib, sorafenib or bevacizumab (n= 44) to patients who had undergone upfront nephrectomy (n= 58) [79]. No difference in perioperative complications was noted. In another retrospective study, Thomas et al reported on the perioperative morbidity in 19 patients with RCC who had been treated with targeted therapies before undergoing nephrectomy [80]. Three patients had complications. The authors concluded that resection of RCC after targeted therapy is feasible and relatively safe in patients with low morbidity, however patients with surgical risk factors are at an increased risk of complications and benefits should be weighed against the risks. A prospective study evaluated the efficacy and safety of presurgical bevacizumab in 50 patients with metastatic clear cell RCC [81]. This study showed that there was an increase in both nonserious and serious perioperative wound healing delays in bevacizumab pretreated

patients compared to historical controls, but treatment reinitiation was not delayed in most patients.

Laboratory studies and animal models raise some concerns about the use of antiangiogenic agents as neoadjuvant options. One such concern is the possibility for “metastatic conditioning” if these agents are given too early. In a mouse model for metastatic breast cancer, treatment with sunitinib for short periods of time decreased OS and accelerated metastatic tumor growth [85]. Identical results were also obtained with a mouse model of pancreatic neuroendocrine carcinoma and glioblastoma [86]. Whether this applies to RCC and to humans is unknown, but these results are concerning in that they recapitulate neoadjuvant treatment: therapy is typically administered for a short period of time, and then discontinued during the recovery period from the nephrectomy. The reason for this conditioning is unclear but could stem from the upregulation of proangiogenic factors in response to treatment [87], recruitment of bone marrow derived cells, or as a consequence of the diffuse injury caused by the non-selectivity of sunitinib.

Another concern is that a delay in treatment imposed by neoadjuvant therapy might preclude some patients from undergoing nephrectomy. In this scenario, some patients' performance status might worsen between the time of initial treatment and progression of the disease, making them poor surgical candidates. In a study performed at the Cleveland clinic foundation, 47 % of patients who were treated with sunitinib as a neoadjuvant treatment had progression of their primary tumor size [72].

In summary, the use of neoadjuvant therapies in RCC should be still considered experimental. Prospective trials which are performed with correlative tools that permit investigators to accurately measure the status of the circulating microenvironment are needed to further develop this paradigm. Although these tools are currently in development [88], they require some further work before they are robust enough to truly informative.

Conclusion

The treatment of RCC has witnessed significant changes over the last 5 years and multiple clinical trials are assessing the role of the newly introduced target therapies in the adjuvant setting. It is hoped that these agents will result in improved outcomes. Development of the neoadjuvant paradigm is somewhat further behind, and safety of this approach can be extrapolated from results obtained in mRCC.

We need to think carefully about the characteristics of agents required to be effective in the adjuvant and neoadjuvant setting. For the adjuvant setting we need agents that can eradicate circulating tumor cells or micrometastases. In the neoadjuvant setting, we need agents that can downsize and downstage primary tumors. The currently used agents are focused on blocking VEGF signaling and mTOR activity, which may or may not be the best approach. In addition these agents are still fairly nonspecific and can result in toxicities related to either their on-target activity or from unintended off-target tyrosine kinase inhibition. A number of clinical trials will provide insight into the utility of the currently available agents in the adjuvant setting.

Further advances in this field will depend on the integration of surgical options with careful selection and timing of targeted therapies, and the development of molecular markers that will individualize patient therapy.

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Table 1
Clinical trials of immunotherapy agents after nephrectomy in localized RCC

	Control arm	Year	N	Outcome
IFN-α				
Pizzocaro et al	Observation	2001	247	No difference in 5 year OS (66.5 % in the treatment group vs 66.0 % in the control group)
Messing et al	Observation	2003	558	No difference in recurrence free survival (2.2 years in the treatment group vs 3.0 years control group, p=0.33)
IL-2				
Clark et al	Observation	2003	69 (total) 44 (LA RCC)	No difference in relapse rates (76 % in the treatment group vs 65% in the control group, p=0.73)
IFN-α + IL-2 + 5-FU				
Atzpodien et al	Observation	2005	203	Inferior OS in treatment group (5 year OS of 58 % in treatment group vs 76 % in the control group)
Medroxyprogesterone				
Pizzocaro et al	Observation	1987	136	No difference in relapse rates (32.7 % in the treatment group vs 33.9 % in the control group)
Autologous vaccine				
Jocham et al	Observation	2004	558	Improvement in PFS (5-year PFS 77.4% in the vaccine group vs 67.8% in the control group).
Hsp 96 vaccine(Vitespen)				
Wood	Observation	2008	728	No difference in RFS (37.7% in the vitespen group vs 39.8% in the observation group (p=0.506)

LA: Locally advanced