Journal of BUON **15:** 235-240, 2010

REVIEW ARTICLE

Targeted treatment for metastatic renal cell carcinoma and immune regulation

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Summary

New targeted agents have become the mainstream of treatment in metastatic renal cell carcinoma (mRCC) and substituted the previous cytokine-based therapies. Vascular endothelial growth factor (VEGF) pathway is the principle target for drugs like sunitinib, sorafenib and bevacizumab. As VEGF is regulating dendritic cell (DC) function, inhibition of VEGF results in activation of DCs and a shift towards cellular (type 1) immunity, which is believed to favor cancer rejection. Recent studies have established the immune-stimulating effects of sunitinib that may as well be a marker for effectiveness. On the other hand, sorafenib not only inhibits VEGF receptor (VEGFR) but is also a B-Raf inhibitor (a component of the ras – MAPK pathway) and this leads to downregulation of immune responses. Sorafenib has not yet shown benefit in first-line treatment of mRCC when compared to interferon (IFN)-α and sorafenib-mediated immunosuppression may partially account for that. Mammalian target of rapamycin (mTOR), the target of temsirolimus, is an element of the DC activation pathway. There are no data for in vivo effects of temsirolimus in the immune system. The addition of IFN-α to temsirolimus resulted in inferior outcomes than temsirolimus alone. IFN-α has however still a place in mRCC treatment, as bevacizumab has been approved in combination with IFN-α. New clinical trials address the effects of the combination of cytokines with targeted agents. The immune-modulating effects of targeted treatments may be important in pharmacodynamic outcomes, effectiveness or the development of adverse events.

Key words: immune regulation, renal cancer, sorafenib, sunitinib, temsirolimus

Introduction

RCC affects more than 50,000 patients in the United States each year, accounting for more than 13,000 deaths annually. These tumors account for approximately 3% of adult malignancies and occur in a male-female ratio of 1.6:1[1]. The cell of origin, morphology and growth pattern characterizes RCC histology. Histologically, 4 major RCC subtypes have been identified: clear cell (60-80%), papillary (10-15%), chromophobe (5-10%) and collecting duct carcinoma (< 1%). Clear-cell histology is associated with a better outcome than papillary or chromophobe histology in the metastatic setting, but the opposite is true for localized disease [1,2]. Rare histologies like clear cell carcinoma with rhabdoid features have an even worse outcome [4]. Localized disease is curable with surgery but a third of patients present with incurable metastatic disease. The aim of management (when metastatic disease is present) is palliation, although with the development of the novel targeted agents prolongation of life appears to be a real possibility. The median survival for patients with mRCC before the era of novel targeted treatments was 10-12 months [5]. After the introduction of targeted treatment (sunitinib), reports raise the median survival up to 2 years in patients that have previously failed cytokine therapy [6].

RCC, angiogenesis and immune surveillance

Angiogenesis is important for tumor growth and development as well as for metastatic spreading. RCC is often associated with deregulation of angiogenesis through alterations (mutation or gene methylation) of

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Received 21-07-2009; Accepted 03-09-2009

the von Hippel-Lindau (VHL) tumor-suppressor gene [7], that regulates the expression of the hypoxia-inducible factor alpha (HIF-α). HIF-α is a transcription factor that controls the expression of several pro-angiogenic genes like VEGF and platelet-derived growth factor (PDGF) [8]. The VHL-HIF-VEGF axis is therefore a target for therapeutic interventions in mRCC [9].

DCs are the most potent antigen-presenting cells (APCs) [10] and play a central role in the host's anti-tumor immunity. Many investigators have described the defective function of DCs in tumor-bearing hosts [11,12]. One of the possible reasons for this DC defectiveness is the secretion of VEGF by tumor cells. VEGF is regulating immune responses by inhibiting DCs differentiation, maturation and function [13,14]. VEGF inhibits TLR4-mediated but not pro-inflammatory cytokine-mediated DC maturation [15]. This effect is differentially mediated by VEGF-receptor subtypes (VEGFR1 and VEGFR2) [16] and can be partially reversed by VEGF-trap [17]. Additionally, VEGF inhibits T-cell development and activation, and this may further contribute to tumor-induced immune suppression [18]. Inhibiting VEGF by bevacizumab or VEGFR by the protein tyrosine kinase inhibitors sunitinib and sorafenib may therefore reverse the DCs dysfunction and T-cell activation in patients with mRCC and/or synergize with immunotherapeutic approaches.

We will therefore discuss the rationale of such an approach and the emerging clinical and experimental data.

Treatment for metastatic RCC. From cytokines to targeted agents

Several lines of evidence suggest that RCC is an immune-sensitive cancer. For years, treatment with interleukin-2 (IL-2) or IFN-α was the only treatment available for patients with mRCC [19]. A minority of mRCC patients responds to IL-2 or IFN-α treatment with durable remissions that may even lead to cure in some of them, though this is at the expense of severe adverse reactions [20]. However, these agents may provide only modest increases in median survival [21]. IL-2 and IFN-α have now been largely replaced in the treatment of mRCC by novel agents targeting specific components of the pathways involved in tumor growth and angiogenesis [22]. VEGFR inhibition with the multitargeted receptor tyrosine kinase inhibitors sunitinib [23-25] (Sutent®, Pfizer Inc.) and sorafenib [26] (Nexavar®, Bayer HealthCare/Onyx Pharmaceutical) has proven to be an effective strategy for the treatment of mRCC and both agents are now in clinical practice and being tested in the adjuvant setting. Furthermore, the VEGF ligand-binding monoclonal antibody bevacizumab [27] (Avastin®, Genetech, Inc.) and the mTOR kinase inhibitor temsirolimus (Toricel®, Wyeth Pharmaceuticals) have demonstrated clinical activity in patients with mRCC as well [28]. Recently, everolimus (Afinitor, RAD001, Novartis), another inhibitor of mTOR, was approved for the treatment of mRCC in patients progressing after therapy with sorafenib, sunitinib or both [29] (Table 1).

Table 1. Clinical data regarding 5 principal targeted agents used in everyday practice

Treatment	*ORR %*	*Any reduction in tumor burden, %*	*PFS*	*OS*
Immunotherapy				
High dose IL-2	20-23 [51-55]	NA	3.1 [54]	19 [53]
Low dose IL-2 or IFN-α	10-15 [56-59]	NA	4.7 [59]	12-14 [57]
Small molecular weight inhibitors of VEGFR				
Sunitinib	30-45 [23,24,60]	70-75	11 mos treatment-naïve [24] 8.4 mos cytokine-refractory [23,60]	26.4 mos [62] 21.8 mos [61]
Sorafenib	2-10 [26,61]	70-75	5.7 mos treatment-naïve [62] 5.5 mos treatment-refractory [26]	17.8 mos [63]
Bevacizumab (BEV) monotherapy	10-13 [64,65]	70-75	8.5 mos [65]	NA
BEV+IFN-α	26-31		10.2 mos treatment-naïve [27] 4.8 mos cytokine-refractory [64]	
mTOR inhibitors				
Temsirolimus	7-9 [28,66]	NA	3.7 mos treatment-naïve [28] 5.8 mos pretreated [66]	10.9 mos [28]
Everolimus	1 [29]	60 [29]	4.0 mos [29]	NA

ORR: objective response rate, PFS: progression-free survival, OS: overall survival, NA: not available, VEGFR: vascular endothelial growth factor receptor, IFN-α: interferon alpha, IL-2: interleukin 2, mTOR: mammalian target of rapamycin, mos: months

Cytokine treatment in the era of targeted therapies (Figure 1)

There is preclinical evidence suggesting that combining anti-VEGF therapy and immunotherapy leads to a greater antitumor activity than either agent alone in tumor-bearing mice [30]. IFN-α activates DCs [31] and it may synergize with bevacizumab in more effective stimulation of the immune responses. Interestingly, treatment with bevacizumab was approved in combination with IFN-α, as was the original design of the AVOREN study [27]. However, the AVOREN study had no arm without IFN-α and the benefit of bevacizumab was evident even when combined with very low IFN-α doses [32].

In the ARCC trial (the temsirolimus registrational study) the combination of IFN-α with temsirolimus did not improve responses and resulted in inferior overall survival compared to the temsirolimus monotherapy arm [28]. We have to notice though that temsirolimus is not directly targeting VEGF as the other registered targeted agents. There are data showing that mTOR is crucial for the IFN responses of plasmatocytoid DCs [33], the IL-18 production of DCs [34] and rapamycin can induce DCs apoptosis [35]. On the other hand, mTOR is regulating the TLR4-mediated IL-12 secretion by DCs and rapamycin increases IL-12 production (and cell-mediated immune responses) under these conditions [36]. The exact role of mTOR in DC physiology is still controversial but it seems that it is a component of the pathway that regulates the production of proinflammatory cytokines and shifts the maturation of DCs towards a more Th1-inducing type (high IL-12 and low IL-10 production) [37]. Inhibition of mTOR with temsirolimus and induction of inflammatory immune responses with IFN-α could stimulate Th2 humoral inflammatory responses, counting for the higher incidence of adverse reactions seen in the combination arm of the ARCC trial. Patients in the combination arm experienced more grade 3-4 adverse events and consequently had more delays and reductions in treatment.

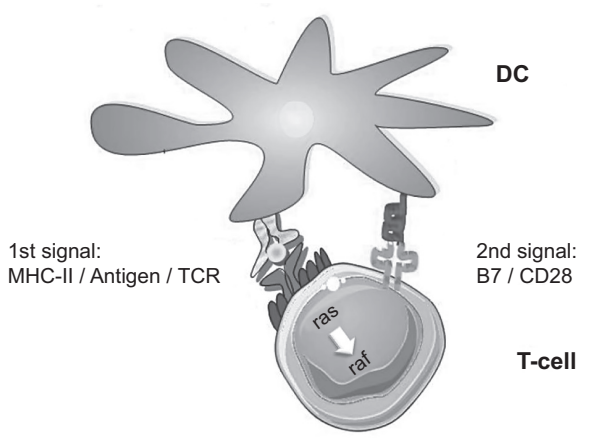

Figure 1. Schematic representation of the immune recognition by a T-cell. Dendritic cells (DCs) present antigen to T-cell receptor (TCR) via a major histocompatibility antigen class II (MHC-II). Downstream events include the activation of RAS – RAF – MAPK pathway, a target of sorafenib. On the other hand, effective antigen presentation requires at least a "second" signal that is usually given via a B7- CD28 interaction. Maturation of DCs and B7 expression is inhibited by VEGF, and sunitinib/sorafenib increase the expression of the costimulatory molecules in the surface of DCs. A third signal that polarizes T-cells towards a TH1 or a TH2 immune response may be regulated by the mTOR pathway.

The question as to what extent cytokine treatment may add effectiveness to targeted treatments remains still unanswered. However, it is intriguing to think that even though targeted therapies perform generally better than IFN-α, they do not lead to cure or the long-lasting remissions that a small minority of patients was experiencing with the cytokine treatment. Therefore, it would be important if it could be possible to identify those patients that may gain a large benefit from cytokine therapy and treat them with IFN-α or IL-2. Alternatively, new ways of combining targeted treatment with cytokines should be explored or attain deeper knowledge of the immune-mediating actions of targeted therapies. Such an approach may lead to better combinations or optimal sequencing and use of anti-mRCC treatments.

Do targeted treatments affect immune surveillance? (Table 2)

In concert with the *in vitro* data, sunitinib augments the *in vivo* immune responses. This is supported by nu-

Table 2. Targeted agents used in the treatment of metastatic renal cell carcinoma and their effects in immune regulation

Targeted agent	*Indications*	*Immune effects*
Sunitinib	1st line mRCC	Increases DCs numbers, maturation and function
Sorafenib	2nd line mRCC	Decreases DCs maturation and function, and T-cell function
Temsirolimus	1st line mRCC (after TKIs)	Probably immune suppression
Bevacizumab	1st line mRCC	In combination with IFN-α, probably IFN effects predominate (immune-stimulation)

mRCC: metastatic renal cell carcinoma, TKIs: tyrosine kinase inhibitors, DCs: dendritic cells, IFN-α: interferon alpha

Table 3. Markers expressed by dendritic cells and effect of targeted agents

Marker	*Function*	*Effects of targeted agents*
CD1a	Myeloid DCs	Increased by sunitinib in responders only, decreased by sorafenib
CD83	Maturation	Downregulated by sorafenib. Sunitinib increases CD83+ DCs in blood
CD80/CD86	Co-stimulation	Decreased by VEGF, reversed by bevacizumab and sorafenib (*in vitro* data). Lipopolysaccharide inductions decreased by sorafenib

DCs: dendritic cells, VEGF: vascular endothelial growth factor

merous recent studies that have addressed several aspects of the immune system in patients with mRCC treated with sunitinib. It has been shown that DC numbers increase to match normal controls after 4 weeks of sunitinib treatment and this is correlated with clinical responses [38]. T-cell activity increases and regulatory T-cells (T-regs) decrease [39]. Patients receiving sunitinib had a significant shift towards Th1 cytokine responses (increasing the intracellular IFN-γ/IL-4 ratio) when peripheral blood mononuclear cells (PBMCs) were stimulated *in vitro* with anti-CD3/anti-CD28 antibodies [40]. In the same cohort of patients, T-regs ($CD4^+CD25^{hi}$) decreased after the administration of sunitinib. The immunostimulatory effects of sunitinib are probably due to the VEGFR inhibition; when the anti-VEGF monoclonal antibody bevacizumab is administered to patients with metastatic lung, breast or colorectal cancer, DC numbers are increased and immature DCs decrease [41]. The allo-stimulatory capacity of DC and T cell proliferation against recall antigens was also enhanced.

Sorafenib, like sunitinib, inhibits receptor tyrosine kinases such as VEGFR-2 and VEGFR-3, PDGFR-β, Flt-3 and c-KIT [42]. However, it targets B-Raf [43] as well, which is a component of the Ras-Raf-MAPK pathway that controls T-cell activation [44]. It inhibits the activation of human peripheral blood T cells by targeting LCK phosphorylation [45]. In a recent publication sorafenib interferes with the function and maturation of the monocyte-derived DCs (MDDCs) by downregulating DC responsiveness to inflammatory signals [46]. DCs migration is reduced, as is their capacity for lymphocyte stimulation. In the same study sunitinib did not impair the induction of primary cell responses and reduced the number of T-regs.

Clinical efficacy and immune functions

Sunitinib has shown anticancer activity and has been approved for the use in fist-line treatment of mRCC. It has a favorable side-effect profile, though in several clinical trials the development of side effects correlated with activity [47,48]. The correlation of clinical responses to immune induction may be an additional marker of activity [37]. The positive effects of sunitinib on DCs functions are of major importance, as DCs are the most potent antigen-presenting cells and the orchestrators of the initial immune responses (Table 3). Whether the immunostimulatory effects of sunitinib account for the higher response rate seen in clinical trials or this represents just a pharmacodynamic readout remains to be answered.

Sorafenib displays different effects on the immune system. Additionally, it has shown lower response rates and could not establish a higher activity than IFN-α in first-line treatment. The sorafenib-mediated immune suppression may partially explain this phenomenon and could argue for trials to combine sorafenib with cytokine treatment [49]. A recent study, however, showed no benefit when low-dose IFN-α was added to sorafenib for first-line treatment in mRCC patients [50].

Finally, bevacizumab has shown benefit in the first-line treatment, in combination with IFN-α, whilst temsirolimus is effective alone and the addition of IFN-α results in inferior effectiveness. These two agents interfere with the DC physiology on a different way and this may explain the different results when combined with IFN-α. Table 2 resumes the effects of targeted therapies on the immune system of patients with advanced RCC.

New targeted treatments have changed the way we see and treat mRCC. There is still room to investigate the role of cytokines and the effects of the new agents on the immune system.

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