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ANTI-ANGIOGENIC AND TARGETED THERAPY IN RENAL CANCER:
VEGF Inhibition in Renal Cell Carcinoma—What have we learned, what are we missing?

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Introduction

Whether by rational design, serendipity, or a combination of both, the last decade of targeted therapy has brought to clinical practice several treatments based on inhibiting vascular endothelial growth factor (VEGF) or its signaling receptors for patients with metastatic renal cell carcinoma (RCC). This concept has been predicated on several important differentiating features of RCC tumors, particularly those with predominantly clear cell or conventional type histology.

- First is the clinical observation that RCC tumors routinely invade and grow within vascular spaces;
- Second, that primary tumors typically, but not always, grow much larger than metastatic sites and that debulking these primary tumors improves long term survival;[1,2]
- Third, these tumors are relatively hypervascular and are commonly associated with both spontaneous central necrosis and bleeding risks;
- Most critically, that genetic alterations in the von Hippel Lindau (VHL) tumor suppressor gene are seen in the vast majority of clear cell RCC tumors.[3].

All of these features support the hypothesis that RCC tumors are unusually dependent upon their tumor microenvironment and in particular, on pro-angiogenic growth factors, most notably VEGF, in order to expand and progress. Also recognizing that, until recently, there were few reliable systemic treatment options for this patient population, it is perhaps clear why VEGF-targeted therapies have been successfully developed for this disease. This short review will focus on reported clinical data and observations for VEGF inhibition in RCC, what we have learned, and what we still need to determine in order to fully capitalize on the significant progress made to date.

Today there are two general classes of VEGF-targeted therapy that have been successfully developed for treatment of RCC patients:

- tyrosine kinase inhibitors of the VEGF receptors (TKIs) and
- bevacizumab the neutralizing monoclonal antibody to VEGF A.

While bevacizumab is specific to VEGF A isoforms, the TKIs range in their level of specificity, from one or more of the VEGF receptors and a few additional class three receptor tyrosine kinases, to multiple receptor tyrosine kinase receptors across several classes (see Table 1 for examples). However, it is difficult to assess to what extent the differences in "off target" profiles and affinities as well as pharmacokinetics explain the variations seen in clinical benefit or adverse event profile of each of these TKI agents.

Progression-free survival

Phase III clinical studies of VEGF-targeted therapies in RCC thus far have primarily demonstrated an improvement in progression-free survival (PFS). The first approvals used either a historical standard of subcutaneous interferon alpha or placebo.[4,5] For example, sunitinib demonstrated a median 11 month PFS versus 5 months for interferon alpha in untreated patients with metastatic RCC (mRCC) , while sorafenib showed a doubling of PFS (5.5 months versus 2.8 months) compared to placebo in a largely cytokine-refractory mRCC population (4, 5). Following this, two Phase III studies investigating interferon alpha with or without bevacizumab demonstrated a significant improvement in PFS in favor of the bevacizumab arms (median PFS 10.2 versus 5.4 months for the European AVOREN study and median 8.5 months versus 5.2 months for the CALGB 90206 study).[6,7] Most recently pazopanib also demonstrated a significant PFS compared to placebo in an untreated, mRCC population (9.2 versus 4.2 months).[8] Ongoing Phase III studies of axitinib, tivozanib, and dovitinib are using sorafenib as a control arm but are still primarily focused on demonstrating an improvement in PFS (clinicaltrials.gov).

Through all of the above referenced studies, the differences seen in PFS have been robust and backed up by secondary endpoints. In terms of objective response rates (ORR), sunitinib, pazopanib, and bevacizumab plus interferon alpha have all demonstrated significant ORR > 20% (4,6-8). In addition, the duration of these responses have been statistically longer than those seen for interferon alpha alone. Across all subgroup analyses in all of these

Overall survival

Despite the robust and consistent pattern of PFS benefit demonstrated for VEGF-targeted therapies in patients with RCC, an overall survival advantage seen has not been clearly seen. All four of the first-line VEGF-targeted Phase III studies reported to date have demonstrated a trend towards an improvement in overall survival, but none have reached statistical significance. In large part this is thought to be due to subsequent treatment with other available VEGF targeted therapy.[7-10] Historically, the median survival of broadly defined patients with mRCC treated with interferon has ranged from 12 to 16 months; however, in the current studies median survival for the interferon control arms have ranged from 17.4 to 21.8 months.[9,10] Nevertheless, some secondary analyses suggest that patients who receive multiple VEGF-targeted therapies may in fact derive a much greater improvement in survival. For instance, in the AVOREN trial, patients treated with sunitinib subsequent to bevacizumab and interferon alpha had a median survival of 43.6 months, and 31.6 months for any second-line treatment in the CALGB 90206 study.[7,10]

Adverse events

Adverse events have been well documented from all these studies and affect several important organ systems including gastrointestinal, cardiovascular, dermatologic, hematologic, renal, respiratory, musculoskeletal and psychiatric, as well as constitutional symptoms. Here the route and class of VEGF-targeted therapy seem to matter. In particular, for orally administered multi-targeted TKIs the most common toxicities include gastrointestinal (diarrhea, nausea, vomiting, mucositis and dyspepsia) dermatologic (including hand foot syndrome, rash), fatigue/asthenia, hypertension, minor bleeding, elevated creatinine, liver function test abnormalities, as well as decreases in white blood cells, platelets and anemia. Some ongoing Phase III studies comparing two TKIs will help determine if one is better tolerated than another. With regards to bevacizumab toxicity in patients with RCC, it is impossible to discern completely from the AVOREN and CALGB 90206 studies how much of the toxicity profile is from bevacizumab versus the combination with interferon; however, phase II studies of bevacizumab alone suggest common toxicities are more limited to fatigue/asthenia, hypertension and proteinuria.[11,12]

Table 1. Tyrosine kinase inhibitors

Agent	Class	Route of Administration	Targets
Bevacizumab	Monoclonal antibody	intravenous	VEGF A isoforms
Sunitinib [17]	Multitargeted TKI	Oral	VEGFR 1-3 PDGFR a,b C-Kit Flt-3 RET
Sorafenib [18]	Multitargeted TKI	Oral	VEGFR 2,3 PDGFR b C-Kit Flt-3 C-RAF B-RAF
Pazopanib [19]	Multitargeted TKI	Oral	VEGFR 1-3 PDGF a,b C-Kit
Axitinib [20]	Multitargeted TKI	Oral	VEGFR 1-3 PDGFR b C-Kit
Tivozanib [21]	Multitargeted TKI	Oral	VEGFR 1-3 FMS-like tyrosine kinase
Dovitinib [22]	Multitargeted TKI	Oral	VEGFR 1-3 PDGFR b C-Kit FGFR 1-3 CSF receptor

Less common but more concerning for this class of therapy are the serious adverse events that have been seen, including potentially life threatening toxicities. Spontaneous, tumor-related and wound-related (dehiscence) bowel perforations, myocardial infarctions (MI), cerebrovascular accidents (CVA), reversible leukoencephalopathy syndrome (RPLS) and life-threatening infections have all been associated with VEGF-targeted therapies.[4-8] Thankfully the event rate for each of these is low (around 1 %) but potentially could be greater with sequential or concomitant treatment. These risks will need to be balanced as we attempt to expand the use of VEGF-targeted therapies into adjuvant settings and combination strategies.

Conclusion

VEGF-targeted therapies are effective individually at delaying disease progression and in all likelihood, at collectively extending survival. Toxicities are broad based and significant but rarely life threatening. However, despite all of the approved therapies, we see surprisingly few complete responses, and the vast majority of patients have disease progression within 2 years. At present, there is no evidence we have cured any additional patients through the use of VEGF-targeted therapy, although there are three Phase III adjuvant studies ongoing with VEGF-targeted therapy in patients with RCC to test this possibility. Despite an enormous effort in development, there is surprisingly little clinical data to help us understand mechanisms of progression in this disease.

In several other cancer types, it is clear that inhibition of a pathway activated by a dominant genetic alteration not only results in improved clinical benefit but also in clear mechanisms of resistance that are selected for within that same signaling pathway. Termed "oncogenic addiction" these cancer types appear to depend upon this critical path not just for primary progression, but for secondary progression even in the setting of prolonged inhibition. Some of these mechanisms have been clearly elucidated, as in the case of c-Kit mutations in gastrointestinal stromal tumors (GIST) or bcr-Abl translocations in chronic myelogenous leukemia (CML); however, other circumstances may be more subtle, but no less addicted. In the case of prostate cancer, the androgen receptor (AR) signaling pathway is frequently activated in castrate resistant prostate cancer and appears to be important to cancer progression, as evidenced by the clinical effects of secondary inhibition of androgen biosynthesis or potent AR inhibition.[15,16]

To what extent VEGF inhibition in RCC results in some of these same patterns of resistance is not known. However, early observations that patients may derive clinical benefit from sequential approaches to VEGF pathway inhibition suggests that either RCC has some elements of VEGF addiction or, at the least, an incomplete mechanism of resistance. What is missing is data with regard the molecular and genomic profiles of resistance to VEGF inhibition and the effect of combined VEGF blockade. Early efforts to combine VEGF-targeted therapy have been associated with unacceptable toxicity (reviewed below) but these efforts should not be disregarded. Strategies evaluating complete VEGF blockade are needed test whether we can achieve durable, complete responses in patients with RCC with VEGF-targeted therapies.

Discussion

Dr. McDermott: Should sorafenib be a drug that experts advocate for use in RCC if all these trials prove that second-generation drugs are more active?

Dr. George: Well, interferon is still FDA approved.

Dr. McDermott: I am not saying remove it from the market, but a general oncologist could think it does not really matter what you use

or when you use it because it is hard to predict benefit and toxicity with these drugs, so you could try whatever you like and if something doesn't work you just go to the next one.

Dr. George: I think we need to begin to understand that RCC can be thought of as a number of different subsets, then begin to figure out profiles for each subset to move forward in a rational manner. Otherwise we are stuck with the NCCN guidelines of just a sheet of recommendations and then lots of Level 2, 3 recommendations to follow.

Dr. McDermott: Right. Recent ASCO data indicate that some groups should perhaps be on a warning list for referral – those people with rapid progression. You should be thinking about clinical trials in those groups of people up front.

Dr. George: We need to think of that subset a little differently They are difficult to study because they do have a very short survival. Identifying those patients even before they fail sunitinib or other front-line therapy would be ideal for planning second line therapy, because if you try to capture them after the fact, you are likely dealing with serious clinical issues such a cord compression and brain metastases that make it difficult to get them eligible for a clinical trial. So that is where I think knowing upfront what their prognosis is and what drug would work best for them would be really helpful.

We have said you cannot combine MTOR with VEGF inhibitors. People have said this is dangerous, and there is no added benefit to the combination. But have we really explored all the combinations? Could the more selective VEGF pathway inhibitors combine better with mTOR inhibitors? What about the dual Tor inhibitors? So maybe we are close and we just have not done the right two combinations on the first pass.

Dr. McDermott: I think we need to think about the biology in order to rationally develop combinations.

Dr. Rathmell: Yes, I agree we are very close, but we are need to understand what causes resistance because ultimately everybody gets resistance to these drugs.

Dr. Atkins: I just want to clarify your statement that people whose disease progresses rapidly on VEGF pathway inhibitors tend to also exhibit rapid disease progression on an mTOR inhibitor. That has not been our experience. I think there is a subset of people who progress rapidly VEGF pathway inhibitors whose disease can respond extremely well to a TOR inhibitor. Thus, this represents an opportunity to possibly tease out at least two populations who might get a different targeted therapy first.

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