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Innovations and Challenges in Renal Cancer

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Overview

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Introduction

In 2010, an estimated 58,000 new cases of renal cell cancer (RCC) will be diagnosed in the United States and 13,000 people will die of this disease.[1] Renal cancer is made up of several different types of cancer, each of which has distinct molecular underpinnings and a different response to treatment. For clear cell carcinoma, the most common variant, three potentially distinct targets and related therapeutic approaches are currently available: immunotherapy, vascular endothelial growth factor (VEGF) pathway blockade, (antiangiogenic therapy), and mTOR inhibition (targeted therapy). Application of these therapies has improved the median survival for patients with advanced RCC from a median of 10 months in 1999[2] to in excess of 2 years.[3] Nonetheless, for patients who either present with or develop metastatic disease the expected 5-year survival rate is still only approximately 10%. Recent research is helping to clarify what can be expected from each treatment approach, which patients are most likely to benefit from particular therapies and opportunities for enhancing the efficacy of each approach. Additional research is beginning to elucidate mechanisms of resistance to various treatment approaches, strategies for treatment sequencing, opportunities and obstacles to combination therapy, as well as potential novel

therapeutic targets. It is envisioned that these efforts will enable rational treatment selection and lead to additional improvements in not just median overall survival but also in the proportion of future long term disease free survivors with this disease.

Molecularly Biology of RCC

Approximately 60-80% of clear cell RCC lacks a functional von Hippel-Lindau (VHL) gene as a result of biallelic loss from mutation and/or hypermethylation.[4] The loss of VHL results in the accumulation of HIF (even in normoxic conditions) leading to increased expression of hypoxia regulated genes such as VEGF. This feature is thought to account for the unique initial sensitivity of RCC to VEGF pathway antagonists. One approach to improving therapy is to identify genetic alterations that cooperate with VHL loss in clear cell kidney cancer. Mounting evidence suggests that one of the relevant genetic alterations might be the inactivation of HIF1α on chromosome 14q. Recent data suggests that clear cell tumors with HIF1α loss (those that are HIF2 only) are more aggressive.[4] This, together with earlier work from the Kaelin Laboratory,[5] suggests that HIF2 is the major oncoprotein in RCC while HIF1 actually functions as a tumor suppressor. The view that HIF1 is a tumor suppressor in RCC is supported by other experiments showing that downregulation of HIF1, using shRNA, promotes VHL-/- RCC growth in vitro and in vivo, whereas reintroduction of HIF1 into the approximately 40% of VHL-/- RCC that do not otherwise express HIF1 suppresses their growth in vitro and in vivo (Shen, Kaelin et al personal communication). Thus efforts to target HIF2α appear particularly warranted in this disease.

Other potential targets exist on chromosomes 5 and 8 where chromosomal amplifications have frequently been noted.[6] An integrated analysis aimed at identifying genes in amplification peaks that are consistently over-expressed in tumors with amplifications, confirmed MYC as a potential target of 8q amplification and identified candidate oncogenes in the other regions. Similarly other potentially relevant genes have been identified within the 5q amplification region. Thus, clear cell RCC may soon be further subdivided into multiple subsets based on sophisticated molecular profiling which have prognostic and therapeutic relevance. Understanding the relevance of various subclasses with regard to current and future therapies will require more robust approaches to integrating molecular profiling into current and future clinical trials.

Immunotherapy

Immunotherapy with high dose interleukin 2 (HD IL-2) was first approved for the treatment of patients with RCC in 1992 due to its ability to produce durable complete responses in a subset of patients. However, the toxicity, complexity and unpredictable efficacy of this therapy has limited its use over the years to patients with excellent functional status and access to facilities with expertise and comfort in administering this treatment. In light of the multiple new treatment options for patients with RCC, efforts to update the current efficacy of HD IL-2 and better define those patient populations most likely to benefit have become a priority. Recent studies suggest that that IL2 remains active in the era of anti-angiogenic and molecularly targeted therapy with response rates close to double that reported in the original studies leading to its FDA approval, and that opportunities for improving patient selection still exist.[7]

Given the toxicity and limited efficacy associated with HD IL-2, exploration of novel immunotherapy approaches has also become a priority. Better understanding of immune regulation and mechanisms of tumor induced immune suppression have led to more targeted immunotherapy approaches. Studies with CTLA4 antibodies that block immune regulation and PD1 antibodies that block tumor induced immune suppression have shown considerable promise in the treatment of patients with advanced RCC.[8, 9] Additional development is warranted in both single agent and combinations. It will be very important to select the appropriate patient characteristics and include biomarker studies in those trials in order to identify the most responsive populations.

Anti-angiogenic and Molecularly Targeted Therapies

Therapy targeted at the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways has revolutionized the treatment of patients with advanced RCC. Six agents, including four VEGF pathway inhibitors (sorafenib, sunitinib, pazopanib and bevacizumab) and two mTOR inhibitors (temsirolimus and everolimus) are now approved in the United States for treatment of patients with RCC.

Although the VEGF blockers have different properties, all have been shown to produce tumor shrinkage in 50-70% of patients with cytokine refractory RCC. Sunitinib and bevacizumab plus interferon alpha (IFN) have shown significant improvement in response rate and progression free survival (PFS) relative to IFN alone in treatment naive patients.[10, 11] By contrast, sorafenib and pazopanib have shown PFS benefit relative to placebo in either cytokine refractory patients (sorafenib) or a mixture of treatment naive or cytokine refractory patients (pazopanib).[12, 13] An overall survival benefit has not been firmly established for these agents. However, this is thought to be related to crossover of IFN or placebo treated patients in the clinical trials to VEGF pathway inhibitors after disease progression, as the median overall survival for the study population as a whole has increased from the previous standard of 10-13 months with IFN to 18-24 months.

More selective and potent VEGFR tyrosine kinase inhibitors such as axitinib and tivozanib are currently under investigation and may offer opportunities for enhanced efficacy with reduced "off target" toxicities relative to currently approved agents.[14, 15] In addition, current data suggests that the VEGF pathway inhibitors can exhibit substantial activity when used in sequence perhaps highlighting the potential distinct effects of these agents. However, other data suggests that even the same agent can be active if re-administered after a "drug holiday" supporting the reversibility of resistance mechanisms and the likely pre-eminence of the VEGF pathway in driving RCC progression.

The mechanisms underlying the activity of mTOR inhibitors in RCC is less certain. mTOR inhibition has been shown to downregulate HIF within VHL-defective tumor cells as well as blunt VEGF signaling. In addition, VHL-defective cells are

known to be highly sensitive to drugs, such as the mTOR inhibitors, that induce autophagy.[16] This latter effect may explain why temsirolimus has shown its greatest benefit, prolonging overall survival relative to IFN, in patients with poor prognostic features,[17] while everolimus has shown its principal benefit, delaying PFS relative to placebo, in patients whose disease has progressed following sunitinib, sorafenib or both.[18] However, other data suggest that mTOR inhibitors may exhibit their most profound effects in non-clear cell tumors (presumably with wild-type VHL) [19] and in tumors with upregulation of pS6, a marker of mTOR activation.[20] Thus, the activity of the mTOR inhibitors in these other settings or relative to VEGF inhibitors in either general or selected patient populations requires further exploration.

Additional data suggest that rapalogs, such as everolimus and temsirolimus, primarily inhibit TORC1. This isolated inhibition can allow for feedback upregulation of AKT and TORC2 perhaps promoting resistance and possibly even accelerating disease progression. This may be particularly relevant in RCC as TORC2 activity can lead to upregulation of HIF2α. Preclinical studies in RCC xenografts have documented superiority anti-tumor activity of dual TORC1, TORC2 and PI3kinase inhibitors such as BEZ235 relative to rapamycin as well the its ability to block HIF2α.[21] Thus, BEZ235 and other agents that inhibit both TORC1 and TORC2 (and possibly PI3 kinase further upstream in the pathway) may have significant activity in patients with RCC and deserve further exploration.

Efforts to combine VEGF pathway inhibitors have so far produced extra toxicity necessitating considerable dose reductions in one or both agents.[22, 23] Although more selective agents such as temsirolimus and bevacizumab can be combined at full doses, recent data suggest that the activity and toxicity of the combination may be worse than seen with single agent sunitinib.[24] Thus, realization of the promise of combination therapy may require identification of agents that hit truly non-cross resistant targets, particularly those that are relevant to the development of resistance to VEGF pathway inhibition. Promising non-VEGF targets include MET, FGF and angiopoietin 2 and agents that block these pathways are currently under investigation in patients with RCC. Until these or similar agents in combination with VEGF pathway blockade are able to establish an efficacy and safety benefit relative to VEGF pathway inhibition alone, the management of patients with RCC will likely remain sequential single agents.

Translational Research Studies

Although the impact of VEGF and mTOR inhibitor in RCC has been substantial, several limitations have emerged. Complete and/or durable responses have been only rarely observed, necessitating chronic therapy for the vast majority of patients often with attendant side effects. Furthermore, treatment resistance typically develops after a median of 6-11 months for VEGF inhibitors (< 6 months for mTOR inhibitors) prompting treatment decisions for which little guidance is available. Thus, further research is needed to determine how best to use these agents as well as further improve patient outcome.

Several translational research approaches are attempting to accomplish this goal. Considerable effort has focused on identifying clinical, tissue, blood and imaging based biomarkers that can help inform treatment decisions. To date, progress has been made in identifying clinical and pathologic based prognostic biomarkers[25, 26] and in developing imaging and blood-based pharmacodynamic biomarkers; however, despite good hypotheses, the identification of predictive biomarkers that can help select patients for particular therapies has proven elusive. Current research using treatments in the "neoadjuvant" setting provides a means of understanding mechanisms of action for specific agents as well as validating and/or extending biomarker research.[27, 28] While such studies are touted as offering the potential to determine the activity of a particular treatment before embarking on cytoreductive surgery, determination of the clinical utility of such approaches will be difficult. Nonetheless, it is hoped that evaluation of tissue and imaging correlates from these studies will foster biomarker development and rational development of novel therapies and therapeutic combinations. Current research has suggested that the mechanism of resistance to VEGF targeted therapy is at least in part "angiogenic escape".[29] This angiogenic escape appears to be mediated by increases in a variety of proangiogenic and potentially decreases in angiostatic factors,[30-33] some of which have the potential for being targeted therapeutically. It is hoped that understanding of these mechanisms of resistance will inform efforts to extend to benefit of current treatment approaches.

Conclusion

The treatment of patients with advanced RCC has evolved rapidly over the last decade. Eight agents are now approved for use in the US and many other countries, and patient outlook is considerably brighter. Nonetheless, considerable hurdles still exist before the goal of providing long term survival for the majority of patients can be reached. Promising areas of current investigation include: 1) the identification of more potent inhibitors of existing targets, 2) the identification of novel targets and/or therapeutic approaches, 3) the use of active agents in sequence, in combination or in novel settings, 4) the identification of predictive biomarkers that can help select optimal patients for particular treatments and 5) the discovery of mechanisms of resistance to established therapies and a means of overcoming them. Making progress in these areas will be necessary in order to significantly reduce morbidity and mortality related to advanced RCC.

References

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