IL-6 (S) : 招待講演 6**Progress in Molecular Targeted Therapy for Renal Cell Cancer**

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It has become clear that the biology of clear cell carcinoma of the kidney is driven by upregulation and activation of the VHL/HIF pathway. This leads to transcription and translation of multiple factors, including VEGF, PDGF, and TGF- α important for this cancer's malignant phenotype, including its well known angiogenic characteristics. This has led to the successful development of a number of anti-angiogenic agents including the VEGFR/PDGFR tyrosine kinase inhibitors sorafenib and sunitinib, as well as the VEGF binding agent bevacizumab. These drugs lead to dramatic improvements in progression free survival in randomized phase III studies and early survival data is promising. A number of additional VEGFR/PDGFR pathway inhibitors are undergoing investigation. Toxicities of the VEGF pathway directed agents include hypertension, fatigue, skin rash, diarrhea, and rare serious cardiovascular and cardiomyopathic events.

Another important therapeutic target for clear cell renal cancer is mTOR, perhaps through its role as a translation factor for HIF. A phase III study of the mTOR inhibitor temsirolimus as first line therapy in poor prognosis patients demonstrated a survival advantage over interferon- α . Additional mTOR inhibitors are undergoing investigation and phase II data are promising. Common toxicities of mTOR inhibitors are rash, stomatitis, hyperlipidemia, hyperglycemia, and rare pneumonitis.

Importantly, disease stabilization and tumor shrinkage less than that sufficient for "objective response" is common with both mTOR and VEGF pathway targeted agents. Non-traditional phase II clinical trial endpoints and designs have thus been important for demonstrating anti-tumor activity. Finally, given the availability of multiple effective agents, the role of combination therapy, adjuvant therapy, the relative cross-resistance of the various drugs, and their role in non-clear cell renal cancer are the subject of ongoing trials.