Treatment of Metastatic Renal Cell Carcinoma in 2006: The Bridge from Yesterday to Tomorrow

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Metastatic renal cell carcinoma (mRCC) has been associated with poor prognosis. Standard treatment includes interleukin-2 (IL-2) and/or interferon-alfa (IFN-α); however, only 10–20% of patients obtain any benefit. (1) Prior achievements in management with cytokines include: prognostic models to select patients who benefit, phase III trials showing no benefit for cytokine therapy given in combination compared to monotherapy, and the recognition that specific cell types of mRCC differ in sensitivity to cytokine therapy. (1,2)

The discovery of the VHL tumor suppressor gene, hypoxia inducible factor and their pivotal roles in the growth of clear cell RCC identified a pathway to direct novel, targeted therapy. (1) Small molecule tyrosine kinase inhibitors, monoclonal antibodies and novel agents that target this pathway are being studied. Several show promising activity.

Sunitinib is an oral, tyrosine kinase inhibitor of VEGFR, PDGFR and other receptors. Two phase 2 trials were conducted in patients with progressive mRCC to cytokine therapy. (3) The partial response rate in the initial study of 63 patients was 40%. (3) A second, confirmatory trial conducted in 105 evaluable patients showed a partial plus complete response rate of 44%. (3) A multicenter, phase 3 trial of sunitinib versus interferon-alfa in first-line therapy completed accrual of over 700 patients.

Sorafenib is an oral inhibitor of Raf, VEGFR, PDGFR, and other receptors. Interim analysis of data from a randomized, placebo-controlled phase III trial was reported. (4) Of 768 patients enrolled (sorafenib: n = 384, placebo: n = 385), 2% achieved a partial response and 78% had stable disease compared with 0% and 55% in the placebo group, respectively. (4) Median progression-free survival was 6 months compared with 3 months in the placebo group. (4)

Studies with two other agents, bevacizumab and CCI-779, both report activity as single agents and are being assessed in phase III trials. Bevacizumab is a recombinant monoclonal antibody directed against VEGF that blocks angiogenesis. CCI-779 is an inhibitor of mTOR, which is involved in VEGF mediated angiogenesis.

In summary, cytokine therapy, the mainstay of treatment for mRCC, provides responses in a minority of patients. The VHL tumor suppressor gene targeted approach to mRCC therapy show promise in the treatment of mRCC.

References