PD2-4

Survival Advantage of Temsirolimus Validates a Role for Mammalian Target of Rapamycin (mTOR) in the Biology of Advanced Renal Cell Carcinoma

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Temsirolimus, a specific inhibitor of mTOR, is a novel targeted therapy for the treatment of advanced renal cell carcinoma (RCC). In preclinical models, mTOR increases the mRNA translation of proteins required for tumor cell growth, proliferation, survival, and angiogenesis. An international, randomized phase III trial utilized a risk-based study design and enrolled previously untreated patients with advanced RCC who exhibited ≥3 of 6 predictors of short survival: LDH >15x upper limit of normal; hemoglobin below lower limit of normal; corrected serum calcium >10 mg/dL; <1y from initial diagnosis to randomization; Karnofsky performance status of 60 or 70; and multiple organ sites of metastasis. Temsirolimus (intravenous 25-mg infusion weekly) demonstrated significantly longer overall survival (OS; hazard ratio [HR] for death, 0.73; 95% confidence interval [CI], 0.58-0.92; P=0.08) and progression-free survival (PFS, P<0.01) compared with interferon alpha (IFN; 3 million units [MU], subcutaneously 3x weekly, escalating to 18 MU) in patients with previously untreated RCC and poor-prognostic features (Hudes et al, N Engl J Med 2007;356:2271-81). Median OS times in the temsirolimus and IFN groups were 10.9 mo and 7.3 mo, respectively. The combination of temsirolimus (15 mg weekly) and IFN (6 MU, 3x weekly) did improve PFS, but not OS and was associated with more dose reductions and delays than temsirolimus or IFN alone. Fewer patients in the temsirolimus group developed serious adverse events than in the IFN group (P=0.02). A greater percentage of patients experienced rash, peripheral edema, hyperglycemia, and hyperlipidemia with temsirolimus alone than with IFN alone, whereas asthenia was more common with IFN alone. The results of this trial support the use of temsirolimus as first-line treatment for patients with advanced RCC with poor-prognostic features. Subset analyses by tumor histology showed an OS benefit for temsirolimus vs IFN in patients with clear cell RCC (HR=0.82; 95% CI, 0.64, 1.06) and in patients with other histologies (HR=0.49; 95% CI, 0.29, 0.85), including papillary, suggesting that temsirolimus may be the agent of choice for patients with non-clear cell RCC. The OS advantage demonstrated with temsirolimus validates the importance of mTOR in the biology of advanced RCC.

PD2-5

The Role of Cytokine Therapy at the Age of Molecular Targeted Therapy

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Metastatic renal cell carcinoma (RCC) is currently one of the most treatment-resistant malignancies. However, significant advances in understanding the molecular mechanisms underlying RCC have led to the development of rationally designed therapies. To date, the vascular endothelial growth factor receptor (VEGFR) pathway has been the most promising target, and two agents (BAY 43-9006 and SU11248) that inhibit not only VEGFR, but also other receptors including the platelet-derived growth factor receptor (PDGFR), FLT3, KIT, or Raf kinase, were approved by FDA for advanced RCC. In addition, CCI-779, a novel mTOR inhibitor, was also recently approved by FDA for advanced RCC. On the other hand, although immunotherapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2) has been generally considered as the standard of care in RCC, a limited subset of patients with metastatic RCC obtain clinically meaningful benefit from IFN-α and/or IL-2 therapy. In addition, recent phase III trials for advanced RCC showed the advantage of SU11248 and CCI-779 against IFN-α. However, recent data also showed the limitation of molecular-targeted therapy. We thus considered the role of cytokine therapy at the age of molecular targeted therapy, and reached two possibilities regarding the way to use IFN-α. [1] IFN-α in combination with molecular targeted therapy (Gollob JA et al, JCO, 25:3288, 2007). [2] IFN-α therapy for good responders (Ito N et al, JCO, 25:2785, 2007). We would like to show the two possibilities in our part, including our basic and clinical data.