Antiangiogenic Therapy for Advanced Renal Cell Carcinoma

Edited by Gary Hudes, M.D., Brian Rini, M.D. and Sandy Srinivas, M.D.

Renal cell carcinoma (RCC) affected an estimated 51,900 Americans in 2007, with 12,890 deaths in the United States in 2007. Most forms of RCC are diagnosed in an advanced stage and are highly resistant to cytotoxic chemotherapy. Roughly 10% of patients with metastatic RCC (mRCC) respond to interferon therapy, whereas only 1% respond to interleukin-2 (IL-2). While a small minority of patients obtain durable remissions from high-dose IL-2, this therapy carries high morbidity and mortality risks. Several new targets have been identified in advanced RCC. Angiogenesis is induced in tumor cell proliferation. In a pivotal phase 3 trial involving 750 previously untreated mRCC patients, the addition of BV to interferon significantly increased median PFS by 3.8 months vs. interferon alone (9.6 mo. vs. 5.8 mo., P<0.001). Sorafenib improved PFS compared with placebo in a phase 3 trial of previously untreated patients (median PFS: 5.5 mo. vs. 2.8 mo., P<0.001). Overall survival (OS) at the final analysis was not different between the groups (66% vs. 63%; P=0.18). Both sorafenib and temsirolimus are broadly approved for advanced RCC and current strategies for optimizing its therapy.

Clinical Evidence for Antiangiogenic Agents in mRCC Tyrosine Kinase Inhibitors

Sunitinib and sorafenib are oral multi-kinase inhibitors that exert antitumor effects through the inhibition of VEGF and PDGF receptors. After PDGF is released from normal vascular and stromal cells, the wild-type VHL protein prevents uncontrolled angiogenesis by promoting the degradation of hypoxia-inducible-factor (HIF-1α), a transcription factor activated in response to tissue hypoxia. In renal tumors with mutated VHL, HIF-1 accumulates in the cells, triggering production of proangiogenic growth factors, most notably vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These proteins bind to specific endothelial cell surface receptors (VEGFR, PDGFR), activating mitogenic signaling pathways that induce endothelial cell proliferation, migration, and capillary tube formation.

In the Editor-from-the-Front Page

This CME activity is jointly sponsored by The Angiogenesis Foundation and Boston University School of Medicine. Guests editors: Gary Hudes, M.D., Brian Rini, M.D. and Sandy Srinivas, M.D. Common toxicities with sunitinib and sorafenib therapy include diarrhea, fatigue, hand-foot skin reactions, and hypertension. The development and presentation of the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the Joint Accreditation for Continuing Medical Education (JACME) by the American Academy of Family Physicians, American Academy of Neurology, and American Academy of Ophthalmology has been accredited by the ACCME to provide continuing medical education for physicians. The CME activity is designed to ensure that the physician will be better able to manage patients with advanced RCC and current strategies for optimizing its therapy. The CME activity is intended for physicians who practice internal medicine and primary care with a special interest in renal cell carcinoma. The activity is certified by the ACCME to provide continuing medical education for physicians. The CME activity is designed to ensure that the physician will be better able to manage patients with advanced RCC and current strategies for optimizing its therapy. This CME activity is intended for physicians who practice internal medicine and primary care with a special interest in renal cell carcinoma. The activity is certified by the ACCME to provide continuing medical education for physicians. The CME activity is designed to ensure that the physician will be better able to manage patients with advanced RCC and current strategies for optimizing its therapy. The CME activity is intended for physicians who practice internal medicine and primary care with a special interest in renal cell carcinoma. The activity is certified by the ACCME to provide continuing medical education for physicians.
Targeting Cells and Pathways in Renal Cell Carcinoma

Most cases of clear cell renal carcinoma arise from mutations in Von Hippel-Lindau (VHL), a tumor-suppressor gene that under normal conditions, controls tissue oxygen levels through degradation of the hypoxia-inducible factor (HIF). With the loss of functional VHL proteins, the HIF-1 gene that, under normal conditions, controls tissue oxygen levels through degradation of the hypoxia-inducible factor (HIF). With the loss of functional VHL proteins, HIF-1α accumulates in the cells, inducing a cellular signaling cascade that results in overproduction of numerous proangiogenic growth factors. Antiangiogenic agents target this overexpression of growth factors.

1. **Endothelial Cell:** The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis, vasculogenesis, and lymphangiogenesis.

2. **Pericyte/Parenchymal Cell:** Platelet-derived growth factor (PDGF) and its receptor PDGF-RB mediate vessel maturation.

3. **Tumor Cell:** Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

**Targeted Agents:**
- Axitinib (AG-013736)
- AZD2171 (Pacritinib)
- Bevacizumab (Avastin)
- Erlotinib (Tarceva)
- Everolimus (RAD001)
- Pazopanib (GSK766964)
- Sunitinib (Sutent)
- Sorafenib (Nexavar)
- Temsirolimus (Torisel)
- Vemurafenib (Zelboraf)

**Targeting Tumor Angiogenesis:**

1. **Incipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.**
2. **Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype.** This occurs in response to gene mutations and hypoxia.
3. **Angiogenic vessels form tubules and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.**
4. **Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.**
5. **Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to central hypoxia. Vessel hyperpermeability results in tumor edema.**

**Pathways:**
- **Hypoxia**
- **VEGF**
- **PDGF**
- **FGFR**
- **Ras**
- **Akt**
- **eNOS**
- **MEK**
- **ERK**
- **PDGF-R**

**Additional Growth Factors:**
- **Kit**
- **Flt-3**
- **FGFR**
- **EGF**
- **VEGF**

**Cell Cycle:**
- **CDK**
- **p21**
- **p53**
- **Rb**
- **cyclin**

**Integrin Targets:**
- αβ1
- αβ2
- αδβ1
- αδβ4

**Metastases exit through the tumor vasculature to the systemic circulation.**

**Inflammatory cells and stromal cells also release growth factors.**

**How blood vessels sprout:**
- Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation.
- Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific integrins. Monoclonal antibodies directed against αβ1 integrin may interfere with blood vessel formation by inducing apoptosis in proliferating endothelial cells.

**Endothelial Progenitor Cell (EPC) from bone marrow**

**Local Endothelial Cells:**
- Progenitor cells differentiate into mature endothelial cells, forming new blood vessels.

**Basement Membrane:**
- Integrin may mediate adhesion and migration of EPCs.