

Improved Treatment Options for Metastatic or Advanced Renal Cell Carcinoma

Mario Sznol, MD and Harriet Kluger, MD

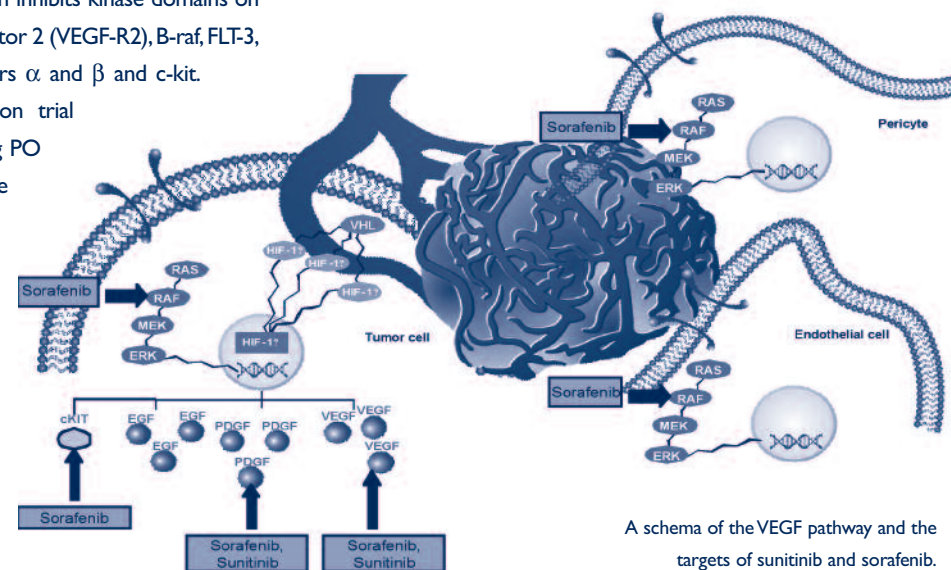
Since December 2005, two new anti-angiogenic agents, sorafenib and sunitinib, have been approved by the FDA for the treatment of metastatic Renal Cell Carcinoma (mRCC). The clinical data indicate that these agents provide meaningful benefit to patients and thus represent the first advance in treatment of mRCC since interleukin-2 was approved by the FDA in 1992.

Sorafenib (Bayer, Inc. and Onyx Pharmaceuticals, Inc.) is a small molecule tyrosine kinase inhibitor, which inhibits kinase domains on vascular endothelial growth factor receptor 2 (VEGF-R2), B-raf, FLT-3, platelet derived growth factor receptors α and β and c-kit.

In a novel, randomized, discontinuation trial design, it was given at a dose of 400mg PO BID to 202 patients with RCC that were either unable to receive cytokine therapy, or had cytokine refractory disease. 144 patients (71%) had tumor shrinkage or disease stabilization at 12 weeks, and 4% had independently confirmed partial responses. After 12 weeks on therapy, patients that did not have progression or did not have > 25% reduction in tumor size by RECIST

criteria (i.e. those with stable disease) were randomized to receive placebo or to continue the Sorafenib. Progression-free survival was superior on the Sorafenib arm ($P=0.0087$) (1). Subsequently, a phase III international trial randomized 905 patients with mRCC to receive placebo versus sorafenib, and showed that sorafenib doubled the median progression free survival to 24 weeks compared to only 12 weeks for patients receiving the placebo

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Urinary Diversion Following Radical Cystectomy

John W. Colberg, MD

Advances in surgical techniques have dramatically changed the options patients and surgeons have when confronted with the need for urinary diversion following radical cystectomy. Radical cystectomy with urinary diversion is currently the standard treatment for invasive bladder cancer. Approaches to urinary diversion have developed along three distinct pathways: (1) a noncontinent form (ileal conduit), (2) cutaneous continent

reservoir (heterotopic urinary diversion), and (3) bladder substitution (continent orthotopic neobladder).

The ileal conduit is constructed using a small piece of terminal ileum isolated from the gastrointestinal tract. One end is closed and the other is brought through the abdominal wall as a stoma. The ureters are implanted into the conduit in a refluxing manner. The patient must maintain an external

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Editor's Letter

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It is with great pleasure that I present to you the inaugural issue of *Advances*, focused on Prostate and Urologic Cancers. This publication is designed to update urologists, medical oncologists, and radiation oncologists with the latest in research breakthroughs, clinical trials, and state-of-the-art treatment both internationally and at Yale Cancer Center.

It is an exciting time to be a scientist investigating cancers or a clinician treating cancers of the genitourinary tract. There has been an evolution in our basic science understanding of the tumorigenesis of many GU malignancies.

Chemotherapeutic options for patients with advanced prostate and kidney cancer have recently shown increased promise. The FDA recently approved two separate small molecule drugs that work to block the VEGF receptor for the treatment of metastatic renal cell carcinoma. These are the first two drugs to be accepted for clinical use to treat mRCC in over a decade. In addition, a docitaxol regimen was shown to improve survival in patients with metastatic hormone refractory prostate cancer, a population that has proved difficult to treat.

Radiation treatment has seen a change both in the dosing that can safely and effectively be delivered to the prostate and in improvements in the modality of the radiation delivery. These advances can help to thoroughly eradicate prostate cancer cells, yet minimize the effects of radiation to nearby organs.

Many of these breakthroughs are highlighted in this inaugural issue of *Advances*. I encourage you to respond with requests for topics to be reviewed, editorial replies, and questions and look forward to hearing from you.

Sincerely,
D. Singh
Dinesh Singh, MD

Intensity Modulated Radiation Therapy for Prostate Cancer

Richard E. Peschel, MD, PhD

Intensity Modulated Radiation Therapy (IMRT) is an exciting new treatment program for early stage prostate cancer. Because of early detection due to PSA screening and public awareness, there has been an extraordinary stage migration (SM) in the diagnosis of prostate cancer, such that over 90% of all new prostate cancer patients have their disease confined to the prostate or the peri-prostatic region at the time of diagnosis. IMRT allows the radiation oncologist to focus higher and higher doses of therapeutic radiation on the prostate and peri-prostatic regions but without producing bladder or rectal damage. This new treatment strategy is called IMRT with dose escalation. The early 5-year results using IMRT with dose escalation for prostate cancer show improved biochemical disease free (bNED) survival rates but with lower complication rates when compared with conventional therapy (1). In addition to SM and better local therapy using IMRT, hormone therapy (HT) used together with IMRT has improved the overall survival rates for prostate cancer patients with high grade and more aggressive tumors when compared with radiation therapy alone (1).

COMPLICATION RATES: EARLY RESULTS

Table I summarizes the Yale Cancer Center complication rates (bladder and rectal) using IMRT for early prostate cancer compared to previous radiation therapy programs used at Yale over the last 30 years. The table clearly documents that complication rates using IMRT are the lowest we have seen in over 30 years of treating local prostate cancer.

FUTURE PROGRAMS

Using breakthrough technology called "image guided radiation therapy," it will

be possible to escalate prostate radiation doses to even higher levels than with IMRT alone. We are entering a new era in terms of successful therapy for local prostate cancer. Within this context, it is vitally important to establish the long-term complication rates and quality of life parameters for these new treatment approaches as we dose escalate to even higher radiation doses using "image guided" techniques. The Department of Therapeutic Radiology at Yale School of Medicine (Dr. Richard Peschel, PI) has received a \$250,000 grant (2006 – 2008) from the Anna Fuller Foundation to continue its clinical research on quality of life parameters using IMRT and image guided radiation therapy for early prostate cancer patients.

Reference

1. Peschel R and Colberg JW: Surgery, brachytherapy, and external-beam radiotherapy for early prostate cancer. *The Lancet Oncology* 2003; 4: 233-241.

TABLE I

Complication Rates using Radiation Therapy for Early Prostate Cancer Patients Treated at Yale from 1974 to 2006

| Treatment | Complication Rate |
|--|-------------------|
| IMRT 600+ patients (1998 – 2006) | 0.8% |
| Transperineal Implant 325 patients (1992 – 2005) | 7.9% |
| Palladium Implant | 4.0% |
| Iodine Implant | 15.0% |
| Conventional External Beam 340 patients (1974 – 1994) | 12.9% |
| Supra-Pubic Open Implant 141 patients (1974 – 1984) | 10% |

CLINICAL TRIALS Prostate and Urologic Cancers



PROSTATE CANCER:

- HIC 0510000719 A Randomized, Double-Blind, Placebo-Controlled Phase III Study of Early vs. Standard Zolendronic Acid to Prevent Skeletal Related Events in Men with Prostate Cancer Metastatic to Bone (CALGB 90202) Wm. Kevin Kelly, DO (203) 737-2572
- HIC 0508000439 A Randomized, Double-Blind, Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone with and without Bevacizumab in Men with Hormone Refractory Prostate Cancer (CALGB 90401) Wm. Kevin Kelly, DO (203) 737-2572
- HIC 0511000831 An Open-Label, Multicenter, Phase I/II Study of Single-Agent AT-101 in Men with Hormone Refractory Prostate Cancer (HRPC) and Rising Prostate Specific Antigen (PSA) Levels who have not Received Prior Chemotherapy Wm. Kevin Kelly, DO (203) 737-2572

BLADDER CANCER:

- HIC 27510 A Phase II Study of Intravenous (IV) Vinflunine in Patients with Locally Advanced or Metastatic Transitional Cell Carcinoma (TCC) of the Urothelium (second line chemotherapy) Jill Lacy, MD (203) 737-1600

RENAL CELL CANCER:

- HIC 05100000723 Phase I Trial of the Combination of Sirolimus and SU11248 (Sutent) in Patients with Advanced Solid Tumors that are Non-curable with Standard Therapy Mario Sznol, MD (203) 785-6221
- HIC 27409 A Phase I Study of 5-Azacytidine in Combination with Interferon-alfa in Unresectable or Metastatic Melanoma or Renal Cell Carcinoma Mario Sznol, MD (203) 785-6221

Prostate and Urologic Cancers Program: The Multispecialty Team

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($P < 0.0001$) (2). Toxicities associated with sorafenib were manageable and included rash, diarrhea, hand-foot syndrome, hypertension, hair loss, itching, nausea, and fatigue.

Sunitinib (Pfizer, Inc.) is another highly potent small molecule tyrosine kinase inhibitor, whose targets include the vascular endothelial growth factor receptors (VEGF-R I-III) and platelet derived growth factor receptors α and β (PDGF-R- α and β). In two single institution Phase II trials, sunitinib (50mg/d for 4 weeks followed by 2 weeks break) was given to 169 patients who had progressed after cytokine therapy (3, 4). The objective response rates on the two studies were 25% and 36%, and the median duration of response was 27 and 54 weeks, respectively. Sunitinib was well tolerated; toxicities included fatigue, diarrhea, nausea, dyspepsia, stomatitis, hypertension, constipation, and decrease in cardiac ejection fraction. Lymphopenia and hyperlipasemia were the most common laboratory abnormalities, but patients did not develop infections or clinical pancreatitis (3). A phase III study comparing sunitinib to interferon- α for previously untreated of mRCC patients revealed an improvement in median survival in sunitinib treated patients from 5 to 11 months (5).

For the first time in many years, newly identified, effective treatment options are available for patients with mRCC, and additional advances appear to be on the horizon.

Other agents, such as bevacizumab (an antibody that binds VEGF), CCI-779 (an mTOR inhibitor), and AG-013736 (another small molecule anti-angiogenic tyrosine kinase inhibitor) have also shown promising activity in mRCC. Both bevacizumab and CCI-779 have been combined with interferon- α and the combinations are being compared to interferon- α in phase III trials. Results of the former trial are expected soon. Results of the latter trial revealed improved overall survival with CCI-779 compared with interferon and the combination of interferon and CCI-779 ($P = 0.0069$) (6). A surgical adjuvant trial for sorafenib and sunitinib is being planned through the national Cancer Cooperative Groups.

There are many important clinical questions regarding the use of these new agents, for example, should the anti-angiogenic agents be given first-line prior to cytokines, which agent should be given first, and will patients respond to sunitinib or sorafenib if they progressed

on the other agent? What is the role of debulking nephrectomy for patients that will ultimately receive sorafenib or sunitinib? Clinical trials will be needed to address these critical patient care questions. The current data suggest that very few patients receiving anti-angiogenic agents will achieve durable complete responses, and most patients will ultimately develop disease progression and die from their disease. Thus, for appropriately selected patients with the clear cell phenotype of mRCC, good performance status, no ischemic heart disease, and otherwise well preserved major organ function, high dose interleukin-2 initially is still the only available treatment that produces durable complete responses, albeit in only 5-10% of patients (7). For those patients that are not candidates for interleukin-2, sorafenib and sunitinib are good options for first-line therapy.

Entry of patients into clinical trials will be critical to build on the modest successes in mRCC observed so far with the new agents. One approach under investigation at Yale Cancer Center is dual blockade of signaling pathways by combining an mTOR inhibitor (sirolimus) with sunitinib. A study is also underway to combine 5-azacitidine and interferon- α , based on the demonstration of synergistic anti-tumor activity in vitro. Phase II studies with novel agents, including new immunotherapeutics, are in the planning stages. For the first time in many years, newly identified, effective treatment options are available for patients with mRCC, and additional advances appear to be on the horizon.

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The Use of Biophosphonates in Prostate Cancer: To Answer the Question, We Need Your Help

Wm. Kevin Kelly, DO

There has been a great deal of controversy about the use of bisphosphonates in prostate cancer. Zoledronic Acid (Zometa) is approved for use in patients with metastatic hormone refractory prostate cancer. However, Zoledronic (Zometa) acid has not been approved for patients with newly diagnosed metastatic prostate cancer and there is no consensus as to whether it should be used in this setting. Some individuals believe that Zoledronic Acid (Zometa) is likely to provide clinical benefit in terms of reducing skeletal-related events in these newly diagnosed hormone naïve patients. However, others are concerned about the unnecessary cost, potential toxicities, and the lack of any clinical data that supports its use in this population of patients. This highlights the importance of doing clinical trials to understand the risk and benefits of giving Zoledronic acid (Zometa) in this setting.

The Cancer and Leukemia Group B (CALGB) protocol 90202: A randomized Double Blinded, Placebo-Controlled Phase III study of early vs standard Zoledronic Acid to prevent skeletal related events in men with prostate cancer metastatic bone is currently open and needs the support of all oncologists to complete this important trial. Eligibility requirements for this trial include:

- Patients who are newly diagnosed with metastatic prostate cancer
- ≤ 6 months of androgen ablation therapy for metastatic disease
- up to 6 months of prior neo-adjuvant or adjuvant hormone therapy is permitted, provided it was discontinued 6 months ago
- calculated creatinine clearance ≥ 30

Treatment consists of intravenous Zoledronic Acid (Zometa) or placebo every 4 weeks, which is provided at no cost, until the patient develops hormone resistant prostate cancer, at which point all patients are eligible to receive open-label Zoledronic Acid (Zometa), which is also provided by the study. Since a placebo is involved, patients must receive their therapy at a CALGB institution or a Cancer Trials Support Unit (CTSUS) approved site, Yale Cancer Center is currently offering this trial to patients throughout the region.

Whether a clinician should or should not use Zoledronic Acid (Zometa) in patients with newly diagnosed prostate cancer is a critical question. Unfortunately, we will not know the answer unless we complete this trial; your help is greatly needed to answer this question. Please call (203) 737-2572 for more information.

pouching system that contains urinary output from the abdominal stoma.

Heterotopic continent urinary diversions incorporate the right colon as the reservoir and the ileocecal valve as the continent mechanism. This form of diversion requires the patient to perform intermittent catheterization several times a day through a small continent stoma on the abdominal wall.

When different treatment options offer similar cancer control & overall survival, the patient's quality of life becomes a very important issue.

Continent orthotopic neobladders, as alternatives to the ileal conduit and heterotopic continent diversion, have evolved over the last 20 years. It is estimated that 80% of men and 65% of women with invasive bladder cancer are candidates for orthotopic bladder substitution following radical cystectomy. The neobladder is constructed from a long segment of small bowel or a combination of the small bowel and large intestine, detubularized, and anastomosed to the patient's urethra. Voiding occurs normally through the native urethra via abdominal straining.

When different treatment options offer similar cancer control and overall survival, the patient's quality of life becomes a very important issue. Evidence exists concerning differences in health related quality of life among patients undergoing continent orthotopic diversion versus heterotopic urinary diversion and ileal conduit. A trend toward higher quality of life among patients undergoing orthotopic neobladders now exists, making bladder substitution an ideal alternative for the select patient requiring urinary diversion. Currently, orthotopic bladder substitution is offered to appropriate patients (men and women) following radical cystectomy. Distinct advantages of this diversion include preservation of continence, avoidance of an abdominal stoma, and maintenance of normal voiding. However, the complex nature of the surgical procedure requires an experienced surgeon and a younger, healthier patient population.

Prostate and Urologic Cancers
advances

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