

Treating Bladder Cancer:

From Primary Tumor to Metastasis

As a Fellow at Memorial Sloan-Kettering Cancer Center (MSKCC), Andrea Apolo, M.D., gained valuable experience in the design and execution of clinical trials for bladder cancer, as well as a passion for this relatively neglected area of clinical research. As a result, she jumped at the opportunity to develop a new bladder cancer program at CCR, accepting a position as Assistant Clinical Investigator and Head of the Bladder Cancer Program in 2010. Less than two years later, Piyush Agarwal, M.D., was recruited from the Henry Ford Vattikuti Urology Institute in Detroit to become Head of the Bladder Cancer Section in CCR's Urologic Oncology Branch. His deep experience with robot-assisted minimally invasive surgeries to resect tumors and reconstruct bladders is combined with an equally strong ambition to make surgery for the treatment of bladder cancer obsolete through molecular therapeutic strategies. Apolo and Agarwal gave CCR connections a first-hand account of their work in the lab and in the clinic to understand and treat progressive stages of the disease.

Piyush Agarwal Starts from the Beginning

The treatment for most bladder (urothelial) tumors, if they are low grade, is surgical resection followed by surveillance. The high recurrence rate generally means routine lifelong surveillance. With disease progression and invasion of the surrounding muscle tissue,

nonspecific immunotherapies and chemotherapies are the only approved options before more radical surgeries become a reluctant last hope.

Working with one of the pioneers of robotic surgery in bladder cancer, Mani Menon, M.D., I developed the expertise to do quite complicated reconstructive procedures with robotic assistance. Use of this technology translates to

smaller incisions, less blood loss, and shorter stays in the hospital. In the most challenging cases of radical cystectomy, we remove the bladder and replace it with a bladder that we construct from bowel tissue. This is standard-of-care for advanced cases and when it works—and we cure someone—it's wonderful. But, even in the most expert hands, this surgery



Piyush Agarwal, M.D., and Mangala Hari Prasad

has a 30–60 percent complication rate; and despite our best efforts, only about half of patients with muscle-invasive disease survive five years.

We haven't had a new FDA-approved drug for bladder cancer since the 1990s. The number of cases is increasing each year and there hasn't been much impact on mortality. But, I see a lot of untapped opportunity to combine advances in our understanding of the molecular drivers of bladder cancer with therapeutic progress that is emerging from other areas of cancer research.

Finding the Drivers

In building up our bladder cancer program at CCR, we have recruited patients with the dual goals of treating them with the best standard-of-care and studying their tumors for possible therapeutic targets. We have found that the epidermal growth factor receptor (EGFR) is over-expressed in many bladder cancers. EGFR overexpression is associated with several cancers;

my own familiarity with it stems in part from my time as a Urologic Oncology Fellow at M.D. Anderson Cancer Center; the former President, John Mendelsohn, M.D., was instrumental in developing cetuximab (now known as Erbitux) to target EGFR for the treatment of lung cancer. But, as we have learned from that cancer and many others, focusing on a single target is seldom sufficient.

Bladder cancer is more prevalent in men than in women, even when you control for effects of smoking and environmental exposures. But, when women develop bladder cancer, it tends to be more aggressive. We think there is an interplay of steroid hormone receptors— androgen receptors (ARs) and estrogen receptors (ERs)—in bladder cancer. ARs are, of course, involved in prostate cancer and drugs like MDV3100 have been developed against them. So, we are analyzing AR and ER expression in bladder tumors, as well as the expression of other steroid hormone receptors, such as those for progesterone and glucocorticoids.

Illumination and Destruction

Meanwhile, Peter Choyke, M.D., and Hitsataka Kobayashi, M.D., Ph.D., in CCR's Molecular Imaging Program have done some beautiful work on a therapeutic approach that uses photoactivation of a molecularly targeted dye to induce tumor cell death. In a paper published in *Nature Medicine* in 2011, they used an infrared light-sensitive dye conjugated to an anti-EGFR antibody to target tumor cells. Application of near infrared light induced phototoxicity only in cells that had bound the dye-conjugated antibodies. The advantage of such a technique for bladder cancer is that the internal bladder surface is accessible through the urethra, making nonsurgical intravesical therapies possible.

We have been extending this work in bladder cancer cell lines, several of which I was able to bring with me from M.D. Anderson, and in other, newer lines which we have generated here at CCR. We've found that the cell lines that express EGFR respond to this photoimmunotherapy approach in a rather exquisite way: a minute or two of exposure to light kills 90 percent of the cells. The response appears to be dependent on the number of receptors expressed and the amount of energy delivered.

Our next step will be to deliver the drug directly into animal models. In parallel, we are also looking at other molecular targets to see if we can take a combinatorial approach to this therapy. If this approach continues to deliver promising results, I foresee a clinical trial in which we use standard techniques (flow cytometry, Western blots) to analyze the surface receptor profile of individual tumors and then develop a cocktail photoimmunotherapy approach to target the cancer cells and spare the healthy ones.

Insights from Tuberculosis?

The pioneering work of Burton Zbar, M.D., (formerly, Chief, Laboratory of Immunobiology, NCI) and Alvaro Morales, M.D., established the use of the tuberculosis vaccine—Bacillus Calmette-Guerin (BCG)—in the treatment of bladder cancer. In cases where the tumor burden is not too high and direct contact can be made with the urothelium surface of the bladder, BCG application appears to elicit an immune response that attacks the tumor as well as the attenuated virus. The use of BCG for the treatment of bladder cancer was approved by the U.S. Food and Drug Administration in the 1990s. However, we still don't completely understand the mechanism of action of BCG in eliciting an immune response.

We want to study this immune response, but in the context of a novel immunological tool. Our colleagues James Gulley, M.D., Ph.D., Chief of CCR's Genitourinary Malignancies Branch, and Jeffrey Schlom, Ph.D., in CCR's Laboratory of Tumor Immunology and Biology, have developed a tumor vaccine—PANVAC—that contains transgenes from two relatively common carcinoma markers, CEA and MUC-1. We will be opening a trial for patients who have elected against bladder removal and would, therefore, normally receive BCG alone. In our trial, half of these patients will receive BCG and the PANVAC vaccine. By studying the immune response before and after treatment, we will hopefully not only learn more about how BCG works but also learn whether we can augment the response.

“One of the challenges with genitourinary cancers and metastatic disease in general is the difficulty of visualizing the cancer, both to discover its extent and to monitor the response to treatment.”

I look at the bladder cancer program at CCR as a spectrum. I focus on primary urothelial disease, including cancers that invade the muscle tissue; my colleague, Andrea Apolo focuses on metastatic bladder cancer. We try to devise therapies coming from both directions along this continuum.

Andrea Apolo Continues the Fight

I initially became interested in bladder cancer while I was a Fellow at MSKCC, working with Dean Bajorin, M.D., a world-class expert on this disease. I really saw the need for more clinical research. In the Western world, bladder cancer is the fourth most common cancer in men and the ninth most common in women. The disease is very aggressive, but has not received the funding or research attention of other “higher profile” cancers. One primary reason is a lack of advocacy and disease awareness. It's a cancer that people don't really talk about. Especially in women, the symptoms are often treated as an infection and diagnosed very late.

I work with the Bladder Cancer Advisory Network (BCAN) to both raise awareness and help build a



(Photo: R. Bacer)

Andrea Apolo, M.D.

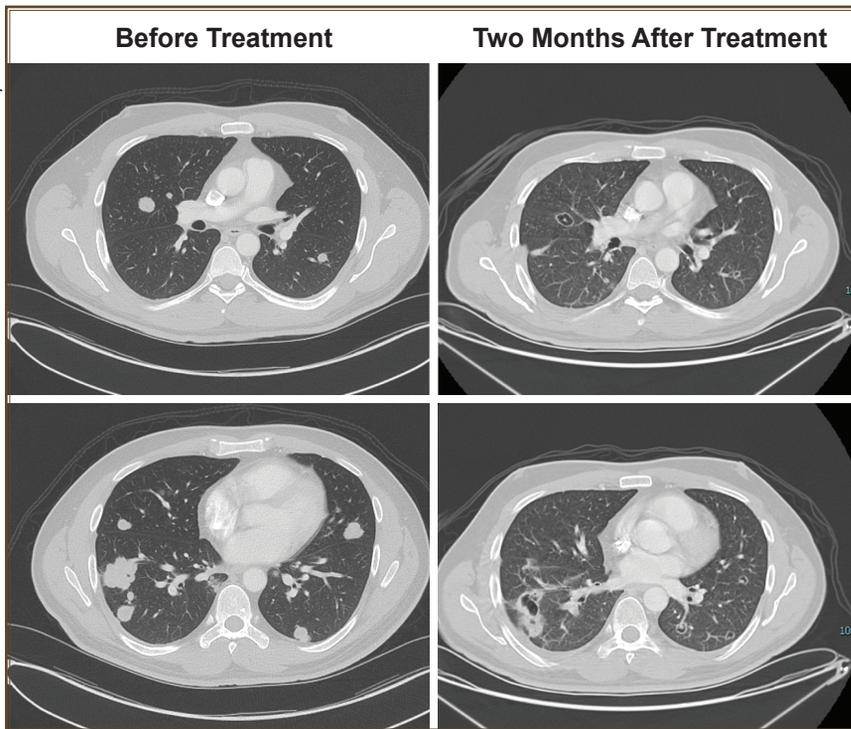
network of investigators across the country through our annual “Think Tank” meeting. At the Think Tank, researchers and clinicians interested in bladder cancer can brainstorm ideas for projects in bladder cancer research and can collaborate on clinical trials. I co-chaired this year's meeting in Colorado and will chair next year's meeting in San Diego. Bladder cancers are very smart tumors with multiple driver mutations that can change over time with treatment. The majority of my patients have metastatic disease, which is currently incurable. Chemotherapy is the only standard-of-care.

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Targeting Blood Vessels

However, we are seeing some very encouraging results in trials of more targeted agents. I am particularly interested in drugs that inhibit new blood vessel formation (angiogenesis) through inhibition of the vascular endothelial growth factor receptor (VEGFR) and their

(Photo: A. Apolo, CCR)



Computed tomography (CT) chest images of a urothelial cancer patient with lung metastases who received cabozantinib.

use in combination with agents that target tumor signaling pathways, as well as with chemotherapy.

As a Fellow at MSKCC, I was involved in and privy to early trials of two anti-angiogenic agents for the treatment of metastatic bladder cancer—sunitinib and bevacizumab—and the results were tantalizing, especially coupled to the fact that we see higher expression of VEGFR in the tissue, blood, and urine of patients.

In the last three years, I have opened five clinical trials for advanced bladder cancer. Currently, I have a phase 2 clinical trial underway of a single agent—cabozantinib—that primarily inhibits VEGF-R2 and the MET signaling pathway. I worked with the company that makes cabozantinib—Exelixis—and NCI’s Cancer Therapy Evaluation Program (CTEP) to design the clinical trial. We have seen some dramatic results. In some cases, tumor shrinkage of over 30 percent, which we just haven’t seen before. [See “Ongoing Trials”]

In collaboration with Donald Bottaro, Ph.D., Staff Scientist in CCR’s Urologic Oncology Branch, we are trying to understand the role the MET pathway plays in the development and progression of bladder cancer. In addition, colleagues from the Laboratory of Pathology, Maria Merino, M.D., and Mark Raffeld, M.D., are looking at the expression of MET in the tissue of all the patients enrolled in the cabozantinib study.

As a result of the impressive responses we have seen, I am currently working on developing a multicenter randomized phase 3 trial, which would be the first such trial in the U.S. of a targeted agent for treatment of urothelial cancer.

Getting a Better Look

One of the challenges with genitourinary cancers and metastatic disease in general is the difficulty of visualizing the cancer, both to discover its extent and to monitor the response to treatment. I have

several ongoing studies with Peter Choyke, M.D., Liza Lindenberg, M.D., and Karen Kurdziel, M.D., in the Molecular Imaging Program, and Les Folio, D.O., in NIH’s Radiology and Imaging Sciences to explore the use of different tracers and imaging modalities.

We have found, for example, that sodium fluoride (NaF) is much more sensitive than the commonly used technetium-99 bone scans in detecting metastatic lesions in the bone. Bone disease in bladder cancer has simply not been assessed. This begs the question of whether the lesions we observe are actually real instances of disease. (We are working on tracers that illuminate particular molecular signatures of disease, e.g. MET expression, but these are still in preclinical development.) So, we do longitudinal studies to follow their progression over time; we hope to follow them for a year, but the reality is that most patients do not survive that long with metastatic disease.

The Program

When I arrived at NCI, there was no bladder cancer program. In the last three and a half years, we have seen over 200 patients come through the program. Particularly for metastatic disease, recruiting patients can be very challenging. The median age is about 70 and about half are former smokers so there are usually several comorbidities and their life expectancy is not long. We have a network of investigators outside NCI that send us patients; and I am also part of a Genitourinary Cancer Multidisciplinary DC Regional Oncology Project (GUMDROP)—a consortium of clinicians who specialize in genitourinary tumors across Maryland, Virginia, and the District of Columbia.

Within the program, we have medical, surgical, and radiation oncology specialists, supported by nurse practitioners and research nurses. We also have several scientists within NIH that are collaborating with us, including a geneticist—Ludmila Prokunina-Olsson, Ph.D., in NCI’s Division

of Cancer Epidemiology and Genetics—who is working on genome-wide association studies (GWAS) of bladder cancer. Together, I think we have the critical mass and momentum to make a real difference for this disease in the years to come.

To learn more about Dr. Apolo’s research, please visit her CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=apolo>.

To learn more about Dr. Agarwal’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=pagarwal>.

Ongoing Trials

Chris Hamilton is participating in his third clinical trial at the NIH Clinical Center for metastatic bladder cancer.

As a communications engineer, Chris Hamilton is used to facing complex challenges. In September 2011, while testing equipment in the deserts of White Sands, N.M., Chris was faced with a new and unanticipated challenge: the symptoms of metastatic bladder cancer. “I don’t smoke, I don’t really drink. I have mostly just worked and had a family. Probably the first outward sign was being tired and I didn’t really recognize that until I started bleeding. Even then, I thought it was an infection.” He flew back to his home in Baltimore, Md., where doctors at Johns Hopkins Medical Institute diagnosed him with stage 4 disease that had spread to his lungs.

“Right after the diagnosis, it was a mad rush to try and figure everything out,” said Chris. He took 3 months’ leave, during which he underwent the grueling standard-



Chris Hamilton and Andrea Apolo, M.D.

of-care chemotherapy regimen and researched his options. He quickly learned that the likelihood of significant remission was low and that he would need other options. He met with clinicians at the NIH, Memorial Sloan-Kettering Cancer Center, and Thomas Jefferson University’s Kimmel Cancer Center. “Unfortunately, there was no clear answer,” said Chris.

When the cancer did return, Chris opted to enter an NCI clinical trial. The first trial he entered was not a good match, but in the meantime, Andrea Apolo, M.D.’s trial of cabozantinib for metastatic cancer opened up. “I was really fortunate she was there to expedite the transition,” recalled Chris. “Once it was clear that the first drug wasn’t working, I was on another trial within two weeks.”

With an expected survival time of only 3–6 months, Chris remained on cabozantinib for 11 months before his

cancer progressed earlier this year. “Probably the best scan I had was around month eight—the cancer was clearing up, under control, and diminished to the extent that it wasn’t really impacting my abilities.” Chris continued working throughout the treatments, taking one or two days per week for clinical visits. “It was light years better than doing chemotherapy.”

Now, Chris is embarking on a vaccine therapy trial conducted by Lauren Wood, M.D., Head of CCR’s Vaccine Branch Clinical Trials Team. Grateful for all the federally funded care he has received and for the time these trials have given him, Chris is concerned that others around the country with lethal cancers are not as easily connected to the right trials. “For fast moving cancers, the process itself can kill you if it takes two months to get on a drug. Having a good advocate can make all the difference.”

(Photo: R. Baer)