Reducing Bladder Cancer Mortality: Early Detection and Novel Therapy for Advanced Disease

On August 9-11, 2012, more than 120 leading clinicians, researchers, patient advocates, and industry representatives convened in Stowe, Vermont, for the 7th Annual Bladder Cancer Advocacy Network Think Tank. Being the only bladder cancer-specific annual meeting in North America, this year’s Think Tank engaged participants representing more than 60 institutions, coming from across the United States and Canada. Bladder cancer is still the fifth most common cancer in the United States with an estimated 73,000 new cases and nearly 15,000 deaths projected for 2012. With no major changes in these statistics over the past 30 years, there continues to be a tremendous need for more bladder cancer research. Since 2006, the Think Tank meeting has focused on creating collaborative opportunities for basic scientists, practitioners, advocates and industry partners to move the field forward.

To set the tone for the meeting, Dr. Julian Adams was invited to present the Keynote Address, “The Development of New Drugs in Cancer—An Integrated Approach.” Dr. Adams, President of Research and Development at Infinity Pharmaceuticals, emphasized the importance of working collaboratively in developing the drug Velcade, a transformational drug for treating multiple myeloma. Velcade was the first cancer therapy approved by the Food and Drug Administration (FDA) in a new class of medicines called proteasome inhibitors. Dr. Adams demystified the process of drug discovery starting with basic cell biology, where he focused on proteasomes, which break down proteins, and proteasome inhibitors which block this process. He found that cancer cells were more sensitive to proteasome inhibitors. After designing a proteasome inhibitor drug which became Velcade, he collaborated with scientific investigators, patient advocacy organizations and the National Cancer Institute to ensure that larger phase clinical trials would be completed, which was key to the ultimate approval of the drug—and improved outcomes for patients.

With the theme of “Reducing Bladder Cancer Mortality: Early Detection and Novel Therapy for Advanced Disease,” the Think Tank panel presentations and interactive discussions focused on three main areas: bladder cancer screening, improving the quality of life for bladder cancer survivors, and challenges in discovering new targets and therapies. In addition, throughout the meeting, participants worked in smaller groups to identify projects for the upcoming year focusing on areas such as improving enrollment and quality of clinical trials, building a bladder cancer tissue bank for future research, evaluating patterns of care for non-muscle invasive bladder cancer, improving the delivery of care for muscle-invasive disease, improving the quality of life for survivors and addressing the impact of health policy changes on bladder cancer. The Think Tank also featured young researchers presenting on significant topics related to the disease.

The meeting concluded with a renewed commitment by all participants to continue this collaboration of exploring new ideas, sharing the latest research and examining multidisciplinary approaches to advancing the diagnosis, treatment and quality of life care for patients with bladder cancer.
Session One: Ways to Move Forward in Early Detection of Bladder Cancer

Yair Lotan, MD, UT Southwestern, Chair
Christine Berg, MD, National Cancer Institute
Timothy Church, PhD, University of Minnesota School of Public Health
Ed Messing, MD, University of Rochester, Moderator
Robert Svatek, MD, UT Health Science Center, Discussion Panel

The goals of cancer screening are to detect the disease earlier than it would be detected with symptoms, treat the disease earlier to improve a patient’s outcome, and decrease deaths due to the disease. There are three major questions to answer before launching large scale trials to test screening for bladder cancer. The first question is how to identify people who are at a higher risk for bladder cancer. The second question is how to identify the optimal method for screening. Current methods include tests to check for blood in the urine and other urinary biomarkers. The third question is whether early detection of bladder cancer can improve survival. A group of investigators from the Think Tank is currently working on designing a study to address these questions. Once these questions have been answered, a large randomized controlled trial can provide more data on how effective screening is for improving patient survival. Two large screening trials discussed were the Prostate, Lung, Colorectal, Ovarian (PLCO) Screening Trial and the National Lung Screening Trial (NLST). The NLST found a 20% reduction in deaths due to lung cancer in people who were screened.

Session Two: Bladder Cancer Survivorship: Opportunities to Advance Patient Care

David Latini, PhD, U.S. Department of Veterans Affairs, Co-chair
Cheryl Lee, MD, University of Michigan, Co-chair
Gerald McNamara, Patient Advocate
Srikala Sridhar, MD, University of Toronto
Linda Jacobs, PhD, RN, Abramson Cancer Center
Joanne Buzaglo, PhD, Cancer Support Community

As medical care and treatments improve there are more cancer survivors and survivorship becomes a more important issue. While it is wonderful that survivorship is increasing, many of these cancer survivors have significant concerns such as fear of recurrence, depression, changes in energy and concentration, and employment issues, which can impact their daily lives. It is important for physicians to recognize these issues, and have tools in place to help address them. A cancer survivorship plan is one such tool, and there is demand among patients for these plans. The plan can serve as a summary of treatment received, offer a plan for follow up care, and provide guidance in overcoming medical and psychosocial challenges that may arise after treatment. The Think Tank Survivorship Working Group developed a Bladder Cancer Survivorship Care Plan in 2011, which has now been piloted at multiple institutions.

Patient and physician perspectives on survivorship care were shared during the session. From the patient perspective, it is helpful for clinicians to refer patients to BCAN and other resources to connect them to survivors who have already had treatments and procedures. Many physicians want to provide survivorship care, but in a survey cited lack of time, resources, guidelines and knowledge on cancer survivorship issues. Physicians responding to the survey also said that they wanted to have information about all relevant advocacy groups and community support issues in one place, be it a website or printed materials.
There is a real need for new strategies to discover promising targets and to develop novel therapeutics for advanced bladder cancer. Several areas that were discussed include new molecular pathology techniques to improve on current staging and grading of tumors, novel immunotherapy approaches, improvements in radiation oncology based on the development of preclinical models and genome analysis. Although staging is one of the most important factors in determining bladder cancer outcome, there is a large range of error in staging with many patients having their cancer understaged or overstaged. Also, grading of tumors has changed from grades 1, 2 and 3 to low grade, high grade and papillary urothelial neoplasm of low malignant potential (PUNLMP). Other important factors to consider in the molecular pathology of bladder cancer include bladder cancer stem cells, tumor subclones and the role of the stromal tissue.

Novel Immunotherapy and optimizing radiation oncology are both areas for further exploration in bladder cancer. The goal of immunotherapy in bladder cancer is to drive components of the immune system to infiltrate and attack cancer cells. In practice, specific immune cell receptors have to be activated and the immune response needs to continue until the tumor is fully eradicated. These approaches have been tested in other cancers such as melanoma, ovarian and prostate cancer, but haven’t been extensively explored in bladder cancer. Areas for researchers to further investigate are how to: increase the immune response, better understand the cellular and molecular mechanisms involved in an immune response to attack a tumor, and determine the best therapies and vaccines for engaging the immune response. In optimizing radiation oncology, one approach is to look at using medications that are radiation sensitizers meaning that they preferentially sensitize tumor cells over normal cells to radiation treatment.

Lastly, The Cancer Genome Atlas (TCGA), a coordinated effort to understand the molecular basis of cancer, offers insight for understanding and treating bladder cancer. TCGA involves characterizing and analyzing genome alterations in bladder and other cancers. This will allow for determining which genomic alterations are significant, meaning whether the alteration is a “driver” of cancer development or progression, or merely a “passenger” along for the ride but not directly responsible for disease development. There is still ‘dark matter’ in cancer genomics, meaning that researchers haven’t yet discovered some of the alterations that are drivers of adverse events like cancer. The data produced in this process, expected to be completed in 2013, will be openly available to advance efforts of cancer researchers.

**Supporting Young Investigators**

Four young investigators were awarded John Quale Travel Fellowships to present their research at the 2012 Think Tank Meeting:

Arjun Balar, MD, New York University Cancer Center, presented on targeted therapies and markers to predict response and prognosis for bladder cancer.

Jeffrey Bassett, MD, MPH, Vanderbilt University Medical Center, discussed introducing tobacco screening into urology clinics and using the visit as a teachable moment among bladder cancer survivors.

Eugene Lee, MD, MD Anderson, talked about driving laboratory science based on patient needs in bladder cancer especially adjunct therapies to BCG and chemotherapy.
Armine Smith, MD, National Cancer Institute, presented on combination targeted therapy in treating bladder cancer.

Gil Redelman-Sidi, MD, a fellow at the Memorial Sloan-Kettering Cancer Center, was the recipient of BCAN’s 2011 Raymond and Maria Floyd Award for Bladder Cancer Research and presented on his results. With the help of the award, Dr. Redelman-Sidi conducted research on the role of several oncogenic pathways in determining uptake of BCG by bladder cancer cells. He found that several proteins are important in this process, including: Pak1, Cdc42 and Rac1. He will continue to study these pathways and BCG internalization in cells in vivo and also look to compare BCG uptake into cells with clinical outcomes to determine clinical significance.

Ongoing Collaboration

Attendees at the 2012 Think Tank participated in six different working groups including two newly-formed groups. The working groups met in small-group sessions to discuss ongoing projects and to develop plans for the coming year. Each group presented on their activities to the full Think Tank.

Enhancing Enrollment and Design of Bladder Cancer Clinical Trials

This working group is focusing on how to improve clinical trial design and enrollment. Entering its second year, the working group conducted structured interviews with experienced investigators over the past year to identify the major challenges in conducting bladder cancer clinical trials. The most common obstacle to completing successful clinical trials was poor patient enrollment. A review of recent bladder cancer clinical trials in the last 15 years showed that most trials have been small, nonrandomized, Phase II, and duplicative. In an effort to improve quality as well as coordination and enrollment among investigators, the group is working with BCAN to develop an online dashboard which will serve as a central repository of open bladder cancer trials, available to researchers and the general public.

Translational Science

As it enters its second year, this working group’s goal is to set up a marketplace of ideas, research questions, unique assessment tools and bladder cancer tissue resources. This year the group is focusing on collecting tissues for micropapillary bladder cancer (MPBC), a sub-type of urothelial carcinoma seen in up to 2-5% of all bladder cancers. Overall prognosis is poor and response to BCG and systemic chemotherapy is generally seen as less effective. The working group plans to obtain tissues from multiple institutions to conduct a central pathologic review of MPBC. Once the data is collected, group members can engage in clinical projects, such as looking at whether MPBC responds to intravesical treatment or different types of chemotherapy.

Non-Muscle Invasive Bladder Cancer

This new working group is focusing on evaluating patterns of care for non-muscle invasive disease and identifying potential improvements. Group members are working on many projects, including determining whether a patient’s presentation with gross or microscopic hematuria impacts the stage or grade of bladder cancer; comparing non-muscle invasive bladder cancer surveillance guidelines from the European Association of Urology (EAU) and American Urological Association (AUA); exploring how to define BCG failure and how to treat patients for whom BCG has not been effective; and looking at predicting progression of non-muscle invasive to muscle invasive bladder cancer using molecular markers.

Standardization of Care

As it enters its fourth year, this working group’s goals are to identify current practice patterns for evaluation and treatment of muscle invasive disease and work towards developing a standardized approach. Ongoing projects include a Quality of Care Initiative which analyzed chemotherapy and radiation therapy use at sixteen academic medical centers before and after surgery, and found substantial differences among the institutions. The next phase of the initiative will focus on gaining a better understanding of the reasons behind differences in providing care. New efforts include creating guidelines for standards of care which cover 49 different topics; investigating the
existing multidisciplinary models for providing care and how these models are related to outcomes, patient experience and satisfaction, and clinical decision making; and collaborating with the Survivorship Working Group to develop a patient survey on management of muscle-invasive bladder cancer and patient satisfaction with treatment.

**Survivorship**

Since 2009, this working group has focused on identifying the needs of bladder cancer survivors and designing tools to help address those needs. The working group has developed a Bladder Cancer Survivorship Care Plan, which provides a record for providers and patients of all treatments received, doctors seen, and available treatment resources. The plan has been pilot tested in multiple institutions and the results are being analyzed. The group has also developed a Patient Tool Kit that is available on the BCAN website and features topics such as cystoscopy, transurethral resection of a bladder tumor (TURBT), BCG, radical cystectomy, and urinary diversions. New efforts include increasing awareness of bladder cancer and BCAN’s work among professional associations, including those representing urologic nurses, oncology nurses, psychosocial oncology professionals, and social workers. Another project is to create patient-focused videos covering treatment options and side effects, diversion types and decision making management, and psychosocial support for patients, survivors and caregivers.

**Health Services Research / Health Policy**

This new working group is focused on health policy, quality of care, and comparative effectiveness research issues in bladder cancer. The group’s efforts include evaluating and developing an expanded set of processes for Enhanced Recovery After Cystectomy (ERAS). The group is also examining policy and reporting requirements related to bladder cancer, such as the National Surgery Quality Improvement Program (NSQIP).

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