9th Annual Bladder Cancer Think Tank

Bladder Cancer Advocacy Network

BCAN®

Leading the way to awareness and a cure

Collaborating to Move Research Forward

The Bladder Cancer Advocacy Network hosted the 9th Annual Bladder Cancer Think Tank from August 7 – 9, 2014 in San Diego. It was the largest Think Tank to date with participation from more than 165 leading clinicians, researchers, patient advocates and industry representatives working towards one common goal – to improve the quality of care for those living with bladder cancer. It's an exciting time in bladder cancer research and the panel sessions and working groups reflected this energy. With representation from 40 prestigious institutions and five countries, robust discussions about novel pathways, the unmet needs of seniors, smoking cessation, and advances in immunotherapy illustrated diverse perspectives across the bladder cancer community. The Think Tank sessions generate ideas and strong collaborations in the field bringing innovation to bladder cancer research.

Dr. Clifford Hudis began the meeting with his keynote address speaking about the greatest challenges and opportunities in oncology. Dr. Hudis, President of the American Society of Clinical Oncology, Chief of the Breast Cancer Medicine Service and Attending Physician at Memorial Sloan Kettering Cancer Center spoke about the cost issues in paying for treatments, developing therapies, and investing in research. Dr. Hudis described the need for improved data infrastructure, explaining that medicine is in the 19th century from a data perspective and that better use of electronic records could improve patient outcomes.

Continuing the theme of "Collaborating to Move Research Forward," the Think Tank panel presentations and discussions focused on four topics in bladder cancer: immunotherapy, multidisciplinary clinics and treatment for elderly patients, smoking cessation, and novel targeted therapies. Throughout the meeting participants joined working groups to identify projects such as: smoking cessation support and educational tools; improving use of the Bladder Cancer Clinical Trials Dashboard; developing a database for patients with non-muscle invasive bladder cancer; collecting tissue for a micropapillary bladder cancer database; creating a patient survey network; and launching a clinical trial on upper tract urothelial carcinoma and chemotherapy treatment. The Think Tank also featured young researchers presenting on significant topics related to the disease.

The many advances in understanding bladder cancer at the genome level with The Cancer Genome Atlas and advances in immunotherapy treatment present an opportunity to build on these findings with translational and clinical level research. The Think Tank creates an environment that allows research ideas to expand. The meeting serves as an incubation center to support new ideas and collaboration between participants to accelerate progress in improving diagnosis, treatment, and quality of life for people impacted by bladder cancer.

Session One: Immunotherapy Discussion

Ashish Kamat, MD, MD Anderson Cancer Center, Panel Chair

Trinity Bivalacqua, MD, Johns Hopkins
"Landscape of Immunotherapy for Urothelial Carcinoma"
William Kim, MD, University of North Carolina, Chapel Hill
"Immune Characterization of Bladder Cancer"
Ashish Kamat, MD, MD Anderson Cancer Center
"Predicting Response to Intravesical Immunotherapy"
Daniel Petrylak, MD, Yale School of Medicine
"Anti PDL1 therapy in the treatment of advanced bladder cancer"

There has been a resurgence of interest in immunology in cancer care, paired with advances in the last 10 years in understanding how immune cells are activated and function. The goal of immunotherapy is to generate a specific immune cell response that can destroy the primary tumor and its potential metastases. There has been recent promise in using immunotherapy to treat solid tumors including bladder cancer. Some of the new developments in immunotherapy treatment for bladder cancer include immune checkpoint inhibitors targeting the CTLA-4, PD-1 and PD-L1 pathways, understanding bladder cancer subtypes and immunotherapy, and determining which patients' tumors will respond to Bacille Calmette-Guerin (BCG) therapy.

Immune checkpoint inhibitors provide a potential immunotherapy approach to treating bladder cancer, especially for patients with advanced disease whose tumors have not responded to platinum-based treatment. One example is the PD-L1 pathway where PD-L1 is secreted by the bladder cancer tumor cell, which then shuts off the T-cells and prevents the immune system from attacking the tumor. Researchers can design anti-PD-L1 antibodies to block this pathway. In a recent Phase 1 trial, patients with metastatic bladder cancer whose tumors tested positive for PD-L1 received MPDL3280A, an anti-PD-L1 treatment. During the trial, 43 percent of patients who received the treatment had a positive response and experienced minimal side effects. MPDL3280A has been granted Breakthrough Therapy Designation status by the U.S. Food and Drug Administration (FDA) for treating bladder cancer. There are more studies underway looking at this drug pathway. Although these results are promising, researchers caution that further research is needed to find the best combination of treatments which could include immunotherapy, surgery, chemotherapy, radiation therapy and other options.

Other researchers are looking at better understanding gene expression. One area involves subtypes of high grade bladder cancer, specifically luminal and basal-like subtypes that have similarities to breast cancer, but differences in overall survival and PD-L1 expression. An older immunotherapy option is BCG, which was developed in the 1970s. However, not all patients' bladder cancer tumors respond to BCG. Researchers are trying to predict whether a patient's tumor will respond to BCG. A recent study was able to make this prediction with 85 percent accuracy, but must be confirmed by further research. If there is a reliable way to predict whether a patient's tumor will respond to BCG, the patient's doctor can either recommend BCG treatment or look at other options and avoid unnecessary treatment and side effects.

Session Two: Unmet Clinical Needs in the Elderly: A Multidisciplinary Approach

Matthew Nielsen, MD, MS, UNC Chapel Hill, and Peter Black, MD, Vancouver Prostate Centre, Co-Chairs

Peter Black, MD, Vancouver Prostate Centre
"Unmet Clinical Needs in the Elderly: A Multidisciplinary Approach"
Arti Hurria, MD, City of Hope
"Assessing Older Adults with Cancer: Understanding Functional vs Chronological Age"
Noam VanderWalde, MD, University of Tennessee West Cancer Center
"Multimodality Bladder Preservation: Curative Treatment and the Older Patient"
Robert Svatek, MD, MS, UT Health Sciences Center at San Antonio

"Influence of advanced age in management of patients with non-muscle invasive bladder cancer"

Aging is a complex process that impacts how individuals tolerate cancer treatment and can magnify side effects. This affects many bladder cancer patients as the average age of diagnosis is 73 years and the number of people aged 65 and over is expected to double in the next 20 years. Often people over age 65 are not included in clinical trials making it harder for physicians to apply results and side effect information to treat older patients appropriately. Additionally, although older patients may experience exacerbated side effects, they are also at risk for receiving less aggressive therapy even when appropriate and they could be good candidates to receive alternatives to surgery like chemoradiation.

Although aging is complicated and affects each person differently, some changes in how the body functions are universal but happen at a unique pace for each individual. Consider an analogy to a car – everyone starts life with a full tank of gasoline but each person uses it up at a different rate. Physicians need to be aware of specific changes that occur with aging that impact cancer treatment. A few of the major changes are reduced kidney function measured by creatinine clearance, hearing loss, nerve damage, cardiovascular changes, and bone marrow toxicity. Many of these factors can determine if an individual is eligible for platinum-based chemotherapy treatment. Geriatric assessment should be an integral part of treating bladder cancer in the older population because determining current level of function, evaluating risk in older patients, and predicting toxicity of treatment can help determine the appropriate intervention. In addition to assessment, better guidelines are needed to determine which elderly patients should be receiving more aggressive therapy. Many older patients are not eligible for bladder removal surgery and may not be receiving alternative aggressive therapy such as chemoradiation. Although some clinicians have questioned whether BCG is less effective in treating elderly patients because of a weaker immune system, there is no clinical evidence that this is the case.

Session Three: Smoking and Bladder Cancer: Strategies for Successful Intervention

David Latini, PhD, Baylor College of Medicine, and Cheryl Lee, MD, University of Michigan, Co-Chairs

Pat Boumansour, Patient Advocate
"Survivor Perspective"
Helena Furberg-Barnes, PhD, Memorial Sloan Kettering Cancer Center
"The Genetics of Nicotine Dependence and the Impact on Treatment Outcomes in Bladder Cancer"
Jeffrey Bassett, MD, MPH, Kaiser Permanente Southern California
"The Role of the Physician in Smoking Cessation Initiatives"
Courtney M. P. Hollowell, MD, Cook County Health and Hospitals System
"An Effective Smoking Cessation Intervention Led by Urologists"
Simulation, Discussion and Q&A

Smoking tobacco is estimated to account for half of all cases of bladder cancer and smokers are more likely to be diagnosed with more advanced disease. Genetic factors also play a role in smoking and bladder cancer risk and could be helpful in targeting interventions. Once a patient is diagnosed it is still important to quit smoking to reduce the risk of cancer returning after treatment and avoid other health consequences. There are many benefits to quitting smoking at any time but the time of diagnosis provides a window of opportunity when patients may be particularly motivated to quit and receptive to advice. Doctors should be aware of opportunity and know about useful resources so they can take advantage of the teachable moment to speak with their patients.

Approximately 30-45 percent of newly diagnosed bladder cancer patients are current smokers. There are many health benefits to quitting smoking. The risk of bladder cancer decreases by 30-40 percent in the first 4 years and by 60-70 percent 25 years of quitting. Patients who continue to smoke after being diagnosed with bladder cancer are twice as likely to have a recurrence as those who quit. Additionally, coronary artery disease risk decreases by 50 percent one year after quitting and the risk of stroke is the same as for someone who never smoked at 5 years after quitting.

While many people are aware of the benefits of quitting smoking it is very difficult to do. Each year 44 percent of smokers make an attempt to quit but only 4-7 percent actually quit long-term. While primary care physicians have traditionally been responsible for screening for tobacco use and smoking cessation, now all physicians are encouraged to engage in this task. A serious diagnosis such as bladder cancer can provide an opportunity where patients are motivated to quit and receptive to advice. Health care professionals need to recognize this opportunity and not miss it due to lack of time or expertise in smoking cessation assistance.

The U.S. Public Health Services recommends using the 5 A's: Ask, Advise, Assess, Assist, and Arrange. This approach increases the motivation and willingness of bladder cancer survivors who smoke at diagnosis to make a dedicated attempt to quit as patients who receive advice from their doctor are twice as likely to make a quit attempt in the next 12 months. Professionals recommend that the physician advise every patient to quit smoking in a clear, strong, personalized manner. The clinician should help patients identify in their own words why smoking cessation is personally relevant to them and help them verbalize the risks of smoking and rewards of smoking cessation. While it is important for doctors to speak with their patients about quitting smoking, patients can feel insulted if the doctor implies that they deserved to be diagnosed with bladder cancer because they smoke or have smoked in the past.

Session Four: Targeting Novel Pathways in Bladder Cancer

David McConkey, PhD, MD Anderson Cancer Center, and William Kim, MD, UNC Chapel Hill, Co-Chairs

Seth Lerner, MD, Baylor College of Medicine
"Translational opportunities from the TCGA project in muscle invasive bladder cancer"
Gopa Iyer, MD, Memorial Sloan Kettering Cancer Center
"Identifying Actionable Genomic Alterations in Bladder Cancer"
Ludmila Prokunina-Olsson, PhD, National Cancer Institute
"Identification of heritable genetic risk factors for bladder cancer through genome-wide association studies (GWAS)"
David McConkey, PhD, MD Anderson Cancer Center
"RNA Subtypes of Bladder Cancer and Their Implications"
Maha Hussain, MD, University of Michigan
"Treatment of Advanced Bladder Cancer, Where We've Been and How to Move Forward"
Jonathan Rosenberg, MD, Memorial Sloan Kettering Cancer Center
"Translating genomic findings into clinical practice- MATCH-UP and other efforts"

There are many new and exciting research findings in bladder cancer than can be translated into actual treatment. Understanding bladder cancer at the genome level can help inform drug development and targets for existing drugs. A study of multiple tumor types from The Cancer Genome Atlas (TCGA) found that bladder cancer subtypes can be genetically similar to lung cancer and head and neck cancer. Other research has found bladder cancer subtypes similar to those found in breast cancer that impact treatment recommendations and patient outcomes. In studies where one patient responded exceptionally well to treatment while others did not, genomic analysis can help explain why. Analysis of inherited genes found genetic variations related to the body's detoxification system linked to bladder cancer, which could inform future drug development. A proposed clinical trial will look at genetic mutations in patients' bladder cancer tumors to assign them to different treatments for metastatic bladder cancer. This is an area of great need especially since there has been no change in median survival for patients with metastatic bladder cancer in the last two decades.

Bladder cancer TCGA results have identified numerous genomic alterations to serve as targets for future studies and clinical trials. There will be further results with more tumor samples that could identify additional mutated genes. An analysis of 12 cancer types found that bladder cancer was the most diverse with tumors that could be classified into three pan-cancer subtypes, 1) bladder cancer only, 2) similar to lung adenocarcinoma, and 3) similar to lung squamous cell cancer and head and neck squamous cell cancer. This information can be used for predicting clinical outcomes and treatment recommendations.

Looking at bladder cancer specifically other researchers suggest that muscle-invasive bladder cancers can be grouped into three subtypes: basal, luminal, and p53-like. These subtypes are also related to clinical outcomes and tumor response to chemotherapy. These findings are similar to breast cancer in which there are multiple subtypes that respond differently to treatment options. The basal subtype classified bladder cancer tumors were most aggressive and were associated with the worst survival rates but also responded well to neoadjuvant cisplatin-based chemotherapy. The p53-like subtype classified bladder cancer tumors were most resistant to neoadjuvant cisplatin-based chemotherapy.

Another area of research is on changes in inherited genes. These genetic variants can be studied using genome-wide association studies (GWAS). Bladder cancer GWAS results found 13 significant signals on genes involved in how the body detoxifies and removes carcinogens. Genetic variations can make parts of this process defective resulting in insufficient removal of cancer-causing chemicals and leading to increased bladder cancer risk. Additionally, if a person with specific genetic risk factors also smokes, their risk of being diagnosed with bladder cancer quadruples and is much greater than either having the genetic risk factors or smoking.

Researchers are also looking at patients who responded very well to treatment when most others did not by looking at the genetic basis for the positive response. When a 73-year-old woman had a positive response to Everolimus in a Phase 2 trial where few others had positive responses, researchers used genome sequencing to find that a TSC1 mutation was related to her tumor's positive response. The National Cancer Institute recently launched the Exceptional Responders Initiative to understand the molecular reasons for exceptional responses to treatment in cancer patients. Since typically 1-10 percent of patients respond well to drugs that do not go on to receive approval for the U.S. Food and Drug Administration, researchers will see if changes in gene expression could explain why treatments were effective only in some people.

The next step is to apply findings to clinical trials. New options are needed for treating metastatic bladder cancer since median survival for patients at this stage has not changed in the last two decades and the standard therapy – methotrexate, vinblastine, doxorubicin(adriamycin), and cisplatin (MVAC) – has a complete response rate of only 15-30 percent. The proposed molecular allocation trial to choose therapy for metastatic urothelial carcinoma following platinum-based chemotherapy (MATCH-UP) will use molecular screening to assign patients to different treatments based on their tumor mutations.

Ongoing Collaboration

Attendees at the 2014 Think Tank participated in seven different working 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
Working Group Chairs: Matthew Galsky, MD, Jean Hoffman-Censits, MD

This working group is focusing on how to improve clinical trial design and enrollment. Entering its fourth year, the working group continued efforts to improve quality of clinical trials as well as coordination among investigators by working with BCAN to develop an online dashboard to serve as a central repository of open bladder cancer trials. This online Dashboard is available to researchers and the general public. The Bladder Cancer Clinical Trials Dashboard launched in April 2014 as a tool developed for patients, doctors, and clinical investigators hosted on the BCAN website. The Dashboard provides information about current bladder cancer clinical trials in lay language for easy use by patients. It is searchable by disease state and location of where trials are available. Information about the Dashboard was shared at multiple professional medical meetings and social media outlets. The group is looking to help increase traffic to the site and use of the Dashboard. The group shared thoughts for improving the Dashboard. Future goals include looking at forming a clinical trial alliance of bladder cancer investigators.

Translational Science
Working Group Chairs: Thomas Flaig, MD, Donna Hansel, MD, Ashish Kamat, MD

This working group's goal is to set up a marketplace of ideas, research questions, unique assessment tools, and bladder cancer tissue resources. Last year the group focused on micropapillary bladder cancer (MPBC), a sub-type of urothelial carcinoma seen in up to 2-5% of all bladder cancers with overall poor prognosis. The group continued work in this area this year as well. A survey went out to the Society of Urologic Oncology members with results recently published in *Urologic Oncology*. Several questions came up from the survey including determining the clinically relevant definition of micropapillary bladder cancer and response of MPBC to BCG and systemic chemotherapy. The group has developed an Institutional Review Board protocol and data sharing agreement to facilitate collaboration. The next steps are to finalize data agreements between participating institutions, have a group of pathologists confirm the MPBC cases, and share the data from collaborating institutions. The group will focus on global characterization of MPBC and pathology projects.

Non-Muscle Invasive Bladder Cancer
Working Group Chair: Yair Lotan, MD

Evaluating patterns of care for non-muscle invasive disease and identifying potential improvements is this focus of this working group. The group discussed current needs in bladder cancer research. One identified need was for a large multi-institutional database that can provide data on outcomes for patients with non-muscle invasive bladder cancer. The group is working on developing the database, with a goal of following patients for 2-3 years. The group also discussed supporting research for bladder cancer prevention as well as preventing recurrences and disease progression.

Standardization of Care
Working Group Chairs: Andrea Apolo, MD, Srikala Sridhar, MD, Matthew Kaag, MD

This working group's goals are to identify and define existing standards of care, understand barriers to implementation, and intervene to promote the utilization of existing standards of care. Past projects include the Quality of Care Initiative to evaluate the use of perioperative chemotherapy for muscle invasive bladder cancer. This was a retrospective study with approximately 4,450 patients, 16 centers, and the use of perioperative chemotherapy which was about 34%. The study is complete and a manuscript is being prepared for submission. A second project looked at how medical oncologists manage muscle invasive bladder cancer with a goal of understanding use of perioperative chemotherapy. Despite current evidence, referral rates for chemotherapy remain low and non-cisplatin regimens continue to be used. Another project was evaluating a patient's understanding of treatment for this disease and how the patient felt during treatment. Other projects include standardizing pathology reporting for transurethral resection of a bladder tumor and radical cystectomy specimens, figuring out how well current guidelines are being followed, looking at different ways to measure quality of life in clinical trials, and publishing a handbook for managing bladder cancer. A major discussion in the group was how to move towards multidisciplinary care for bladder cancer. The group is looking at generating a manuscript outlining different models of multidisciplinary care.

Survivorship
Working Group Chairs: Cheryl Lee, MD, David Latini, PhD

Identifying the needs of bladder cancer survivors and designing tools to help address those needs are the main goals of this working group. The group members focused on building on the smoking cessation panel to develop useful educational tools for patients and physicians. The tool for physicians would provide information on useful resources including billing codes and phone numbers. For patients, there will be information on the short and long-term benefits of quitting smoking. The group also discussed the need for more information on how to choose a urinary diversion type following bladder removal surgery.

Patient-Centered Outcomes and Policy
Working Group Chairs: Seth Strope, MD, MPH, John Gore, MD, MS

This working group is focused on health policy, quality of care, and comparative effectiveness. One effort was to get group members involved in policy efforts in other organizations such as the Agency for Healthcare Research and Quality and the American Urological Association's National Surgical Quality Improvement Project which includes developing a care set of pre and post-operative measures. The group appreciated having patient advocates participate and share their perspectives this year. Group members have identified opportunities for collaboration such a BCAN Patient Survey Network that will help with research prioritization and patient engagement and involvement in Patient Centered Outcomes Research Institute (PCORI). Other topics included optimizing cystectomy perioperative care and determining patient-relevant endpoints such as core recovery, symptom burden, and complications. An additional project is developing patient-centered pathology reports.

Upper Tract Disease
Working Group Chairs: Vitaly Margulis, MD, Surena Matin, MD

Designing studies to allow for improved diagnosis and clinical staging of upper tract urothelial carcinoma is the major focus of this working group. The group is planning to launch an upper tract urothelial cancer neoadjuvant chemotherapy clinical trial. The trial will be two parallel Phase 2 trials. The trial has been approved by Eastern Cooperative Oncology Group (ECOG), endorsed by Southwest Oncology Group (SWOG), and the Alliance for Clinical Trials in Oncology, and is pending final NCI approval. The group discussed looking at intravesical chemotherapy after nephrouterectomy and discussed translational endpoints. The group is also involved with a database with a specific upper tract urothelial carcinoma registry.

Supporting Young Investigators

Four young investigators were awarded John Quale Travel Fellowships to present their research at the 2014 Think Tank Meeting:

Philip Ho, MD, MD Anderson Cancer Center
"Stat3 Transgenic Mice as a Model for Human Basal Subtype of Invasive Bladder Cancer"

Tim Lautenschlaeger, MD, The Ohio State University
"Novel Predictive Micro-RNA Signature in the Setting of Selective Trimodality Bladder Preservation Therapy"

Young Lee, PhD, National Cancer Institute
"Characterization of Met Signaling in Urothelial Carcinoma of the Bladder"

Anirban Mitra, MD, PhD, University of Southern California
"Discovery and Validation of Prognostic Genomic-Based Signatures in High-Risk Bladder Cancer Following Cystectomy"

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