Eleventh Prouts Neck Meeting on Prostate Cancer: Emerging Strategies in Prostate Cancer Therapy

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Introduction

The Prouts Neck Meetings on Prostate Cancer began in 1985 through the efforts of the Organ Systems Branch of the National Cancer Institute to stimulate new research and focused around specific questions in prostate tumorigenesis and therapy. Held biannually, these meetings are unique on many fronts. First, the meetings are relatively small, composed of around 75 individuals, divided equally between young investigators and senior investigators. All attendees are encouraged to actively participate through oral presentations, poster presentations, and, most importantly, in the discussions generated in these forums. Second, our policy is to invite the majority of the investigators who have never participated in a Prouts Neck Meeting and to only have 30% of the attendees represent those that have previously attended a Prouts Neck meeting. Finally, the organizing committee for these meetings is selected based on the scientific theme of a particular meeting. The meeting is organized with short presentations and lengthy discussion times.

Over the years, many new concepts related to prostate cancer have resulted from these meetings. In this report, we present an overview of the major topics and themes that were addressed during the most recent meeting, held November 2–5, 2006, in Prouts Neck, Maine, "Emerging Strategies in Prostate Cancer Therapy." The goal of this report is to bring some of the central questions and concepts related to prostate cancer discussed at this meeting to a broader audience with the hope that this will facilitate research in the field and, ultimately, improvement in the therapeutic options for all stages of prostate cancer. The following is a brief summary of the scientific sessions and the discussion that proceeded from the sessions.

Problems with Characterizing Prostate Cancer Patients—What Are We Treating?

One of the central issues in prostate cancer treatment is categorizing patients into treatment groups. To begin the discussion of how best to characterize patients, it is important to start with what we know about the pathology of prostate cancer. Jonathan Epstein (Johns Hopkins Medical Institutions, Baltimore, Maryland) provided a detailed description of what is currently known about the pathology of prostate cancer. Dr. Epstein also described an argument in which he felt the presence of high-grade prostatic intraepithelial neoplasia as the only indicator in a prostatic biopsy does not translate into an increased risk for future positive biopsies in these men. This is based on a number of studies that have shown that the risk of prostate cancer between men with and without high-grade prostatic intraepithelial neoplasia seems to be similar. Another point raised from his discussion was that, although a significant emphasis of this meeting was placed on understanding inflammatory and stromal changes, which seem to be associated with prostate cancer particularly in animal models of the disease, histologically these are not typically evident. This is an important distinction from other cancer types, including breast and lung, where significant stromal events are indeed observed histologically. This potential difference between models of the disease and what is actually appearing within human prostates seems to be a fundamental issue in understanding the pathogenesis of prostate cancer. The infiltration of immune cells into the prostate throughout the process of carcinogenesis seems to be important and fundamentally different from that of other cancers.

Another tool for characterizing men and their risk of prostate cancer, and the aggressiveness of the disease, is the use of prostate-specific antigen (PSA). Stephen Freedland (Duke University, Durham, NC), along with other investigators, discussed the difference between changes in PSA velocity and PSA doubling time and their ability to specifically discriminate between the aggressive and most aggressive prostate cancers. One of the complexities of characterizing prostate cancer is the heterogeneous nature of the disease. This heterogeneity is observed at many levels, including the cellular level, as well as throughout the body. Kenneth Pienta (University of Michigan, Ann Arbor, MI) described his studies examining men who succumbed to prostate cancer and showed that there is a significant pathologic and biological variability between metastatic lesions present even within the same organ site. Despite the extensive heterogeneity at the molecular level leading to an almost frustrating level of complexity, the course of the clinical disease observed seems to progress along only a few pathways. Stated simply, men dying from the disease can be divided into three groups: those with a cancer cachexia syndrome, those with thrombotic syndromes, and men suffering from unbearable pain resulting in a "morphine" death. Dr. Pienta postulated that morbidity could be diminished and/or survival enhanced by targeting therapies to the offending cytokines, even in the absence of a cytotoxic effect on the tumor.

One of the key elements in the characterization of prostate cancer is the determination if the cancer has spread outside of the prostate. Richard Cote (University of Southern California, Los Angeles, CA) discussed the occult spread of prostate cancer to regional lymph nodes removed at the time of radical prostatectomy.

Micromastastases were identified by immunohistochemical analysis of pan-cytokeratins. Using this pattern of staining, 13% to 15% of patients with occult metastases had accelerated progression and death from the disease in comparison with those who had lymph nodes that were truly negative.

Imaging approaches are being used throughout the cancer field to more accurately classify cancers. This same approach is being applied to prostate cancer. The contribution of magnetic resonance imaging/magnetic resonance spectroscopic imaging was discussed by John Kurhanewicz (University of California San Francisco, San Francisco, CA). Dr. Kurhanewicz presented data showing that spectroscopic analyses using endorectal magnetic resonance imaging technology targeting citrate, choline, and polyamine metabolism seem to have promise. The small sizes of the tumors that are typically diagnosed today frequently make the differentiation between the tumor and adjacent normal tissue difficult, and the signals from these can average out distinguishing features of the cancer. A strategy designed to enhance the sensitivity and specificity of magnetic resonance spectroscopic imaging, termed hyperpolarized ^{13}C magnetic resonance spectroscopic imaging, may provide up to a 40,000-fold enhancement of metabolic imaging.

Our understanding of the genetic aspects of prostate cancer has increased significantly over the last several years. Adam Kibel (Washington University School of Medicine, St. Louis, MO) has examined polymorphisms of ~400 genes related to the androgen axis for both prostate cancer risk as well as the risk for developing aggressive disease. As a follow-up to this discussion, Phillip Febbo (Duke University, Durham, NC) presented data on a multiple gene expression model, which appears to predict occurrence after radical prostatectomy. To deal with the heterogeneity of cancer as described before, Dr. Febbo is studying composite gene expression differences found in various pathways. Changes in the expression of members of these pathways are being studied to determine if they are more reliable than the analysis of individual genes. Among the latest studies are those that use gene expression patterns to predict response to chemotherapy. The goal is to use a signature that will help determine specific therapeutic strategies that might be successful in an individual patient.

The final discussion of this session centered on the question of whether or not there is indeed a group of men who do not require therapy for their prostate cancer. Badrinath Konety's (University of California San Francisco, San Francisco, CA) studies have focused on prostate cancer in elderly men of ages ≥75 years. In a population of older patients from the Veteran's Administration Hospital (San Francisco, CA) PSA testing is still actively pursued for a number of reasons, including risk management, patient wishes, and perceived benefit.

Targeting Specific Signaling Pathways in Advanced Prostate Cancer

Much excitement in the field of cancer therapy has been focused on targeting specific therapeutic approaches. This session was devoted to the discussion of potentially relevant targets or pathways and the treatment of advanced prostate cancer. Phillip Kantoff (Dana-Farber Cancer Institute, Boston, MA) began the discussion underscoring the importance of androgen signaling even in castration-resistant prostate cancer. Neil Bander (Weill Medical College of Cornell University, New York, NY) summarized his experience with J591, the first humanized antibody that binds prostate-specific membrane antigen. The antibody is highly sensitive and specific for prostate cancer in detecting both the local disease as well as distant metastases. Current trials include the use of a J591 conjugate, consisting of J591 and a toxin maytansinoid. In these trials, antitumor activity was observed in some patients, although some men did experience modest (grade 2) neurotoxicity. Finally, further targeting of the androgen and estrogen pathways was discussed by Mitchell Steiner (GTx, Memphis, TN). Dr. Steiner presented data supporting the importance of estrogen receptor α in the developing prostate. Toremifene, a selective estrogen receptor modulator, has been evaluated in the prevention of progression of prostatic intraepithelial neoplasia to prostate cancer.

Development of Personalized Medicine for Prostate Cancer

With the current molecular tools, one of the goals is to develop an individual patient signature that can then be translated into personalized medicine for the disease. One of the major problems in prostate cancer that could be resolved using personalized medicine is the fact that 30% to 50% of men that are diagnosed with prostate cancer would have perhaps gone undiagnosed within their lifetime in the absence of current screening methods. More than 90% of men diagnosed with prostate cancer today receive active treatment; one of the most clinically relevant problems today is that overtreatment of the disease is highly prevalent. H. Ballentine Carter (Johns Hopkins Medical Institutions, Baltimore, MD) presented a discussion revolving around the expectant management of men with prostate cancer. Under this strategy, men with very favorable disease are monitored carefully with a well-thought-out strategy. Dr. Carter's data showed that ~30% of those currently on this program end up requiring more definitive therapy for the disease. Robert Vesella (University of Washington Medical Center, Seattle, WA) discussed the fact that 30% to 50% of patients with prostate cancer that has metastasized have disseminated tumor cells that can be isolated from the bone marrow or the circulation. In keeping with the progress seen for research in all tumor types, prostate cancer research is experiencing an explosion in high-throughput techniques such as DNA microarrays. Unfortunately, the informative value of these data is largely determined by the tools and strategies used for analysis. Scott Tomlins (Chinnaiyan Laboratory, University of Michigan, Ann Arbor, MI) presented two novel analytic methods that have provided insight into the development and progression of prostate cancer. Recognizing that not all prostate cancers may be driven by the same initiating genetic event, Chinnaiyan's group developed an algorithm to look for genes strongly activated in a subset of cancers. This approach led to the discovery of gene fusions involving the androgen-regulated gene *TMPRSS2* and *ETS* transcription factors in a majority of surgically-treated prostate cancers.

Targeting Stroma

Emerging evidence suggests that there is a stromal response during prostate carcinogenesis. Key questions focused on in this session included the natural role of the stroma and stromal responses in wound repair and whether these responses are initiated during prostate cancer progression. Additional questions emerged as to whether this stromal response regulates progression of the cancer foci and whether such a stromal response can be targeted therapeutically.

Theodore DeWeese (Johns Hopkins Medical Institutions, Baltimore, MD) opened this session by discussing the possibility

that damage to the prostate tissue by radiation therapy may stimulate a stromal response that mimics wound-healing biology. He pointed out that the prostate stroma is a critical inducer and director of prostate epithelial morphogenesis and differentiation during development. Extending these observations, David Rowley (Baylor College of Medicine, Houston, TX) discussed the phenotypic alterations in stroma as a function of prostate cancer progression. Whereas normal human prostate stroma is composed primarily of smooth muscle and some interstitial fibroblasts, stroma in Gleason 3 foci are composed of myofibroblasts and fibroblasts, with the majority of stroma containing myofibroblasts in Gleason 4 foci. These changes observed in models are distinct from the pathologic observations Dr. Epstein discussed earlier in the meeting. These apparent differences between the human disease and the models being studied have several potential causes including nuances of animal biology and/or a distinct readout of this effect in human prostatic tissue. Whereas the exact cause was not identified, it was agreed that this was an area that needed additional study.

Targeted Therapies

As described earlier in the meeting, a great deal of excitement revolves around the concept of targeting therapies to particular mechanisms of prostate cancer development. One of these mechanisms is the immune system. As presented by Evan Keller (University of Michigan, Ann Arbor, MI), the immune system plays an important role in both tumorigenesis and progression of prostate cancer. When immune homeostasis becomes unbalanced, this may lead to overactivation of the immune system and concomitant inflammation, or it may lead to immunodeficiency. Phillip Arlen (NIH, National Cancer Institute, Bethesda, MD) discussed vaccine strategies for activating immunity to prostate cancer antigens. A key focus was on activating effective antitumor immunity sufficient to reduce regression. A novel antigen, PAGE-4, was discussed as a potential target for immunotherapy. In another potential approach to immunotherapy, Thomas Griffith (University of Iowa, Iowa City, IA) presented data outlining studies on an adenovirus carrying the gene for tumor necrosis factor–related apoptosis-inducing ligand (Ad5-TRAIL). Although this is a more direct cytotoxic approach, there are data to suggest that TRAIL-induced apoptosis delivers antigen to the immune system and activates systemic tumor immunity. Our knowledge of the role of T cells in cancer has been expanding recently. In addition to the recognition that T helper 17 (T_H17) and T regulatory cells provide additional concepts for cancer pathophysiology and therapy, T_H17 cells are maintained by interleukin-23 and promote defense against bacteria and cancer and may promote autoimmunity. Charles Drake (Johns Hopkins University, Baltimore, MD) presented data showing an important role for interleukin-6 and signal transducers and activators of transcription 3 (STAT3) in the progression of transgenic adenocarcinoma of mouse prostate tumors. Impor-

tantly, STAT3 is necessary for the development of T_H17, which is responsible for inflammation in the prostate. Timothy Ratliff (University of Iowa, Iowa City, IA) presented a prostate inflammation model, the prostate ovalbumin–expressing transgenic mouse.

The definition of a cancer stem cell was a subject of discussion. The consensus was that the cancer stem cell is a functional definition and that a key property of a cancer stem cell is the ability of one cell, when introduced into the appropriate *in vivo* environment, to recapitulate the original tumor in both the structure and complexity of cells. The origin of prostate cancer stem cells remains unclear, and whether it is a result of a genetic or epigenetic event in a true stem cell or it is produced as the stem cell progresses further down the differentiation pathway still needs to be resolved.

Central Questions in the Field of Prostate Cancer

As a result of the meeting, it is clear that there are many important questions in the field of prostate cancer that remain unanswered. Among these are: (*a*) What type of prostate cancer should be treated? Are the patients benefiting most from local treatment really those who should not be treated in the first place? (*b*) Is there an "over-diagnosis" of prostate cancer? (*c*) Why has prostate cancer mortality declined? Is it due to natural history or due to changes in screening or effective therapy(ies)? (*d*) What is the inflammatory infiltrate in the prostate and does this play a role in the development of prostate cancer? (*e*) What are the T cell–specific changes associated with prostate cancer? (*f*) Can personalized patterns of gene expression be used? (*g*) What is the role of the stem cell niche in prostate cancer metastasis? (*h*) Is there a prostate cancer stem cell therapeutic target? (*i*) What is the best way to target systemic prostate cancer: antibodies, aptamers, small molecules, others? (*j*) What is the role of gene translocations in prostate cancer? (*k*) Does PSA have a biological role in prostate cancer and, if so, what is it? (*l*) What is the role of the microenvironment, including the stroma, immune and inflammatory cells, neuroendocrine cells, and other aspects, in prostate cancer?

Summary

As is evident from this report, this meeting generated a great deal of discussion about many of the important issues in prostate cancer therapy today. Despite the limited therapeutic progress seen to date, our understanding of the disease has increased significantly and this is now being applied in the clinical setting.

Acknowledgments