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2006 Conference on Innovations and Challenges in Prostate Cancer

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TARGET AUDIENCE

Urologists, medical and radiation oncologists, and other medical professionals involved in the assessment and treatment of prostate cancer patients.

HOW TO OBTAIN CREDIT

● Review the learning objectives below and read the activity (Summary Statement) in its entirety before completing the self-assessment test and registration.
● Fax/Mail: complete post-test, evaluation and registration and fax/mail registration/evaluation as directed on form.
● A certificate will be mailed within 30 days.

LEARNING OBJECTIVE

Following successful completion of this CME activity, participants should be able to: discuss current recommendations for assessing and treating prostate cancer patients with low risk disease, intermediate/high risk disease, rising prostate specific antigen after local therapy and castration resistant disease.

EDUCATIONAL NEED

This educational journal supplement and the summary statement comprising the CME activity have been designed to address the need to: summarize and communicate current recommendations from academic leaders in the field on available and near-term management strategies and therapies for low risk, intermediate/high risk and refractory prostate cancer; reinforce the importance of multidisciplinary consultation to optimize patient outcomes; and highlight information on clinical trials of new therapies that may be of benefit to their patients.

CME SPONSORSHIP

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The program faculty has reported the following financial relationships with commercial pharmaceutical, device and/or biotechnology companies: T. M. Beer: Novacea: consultant, investor, shareowner. P. R. Carroll: DOD: investigator; NCI: investigator; TAP: investigator. A. D’Amico: Nothing to disclose. R. S. DiPaola: Nothing to disclose. M. A. Eisenberger: Celgene: grant; Cell Genesys: consultant; Centocor: grant; GenVec: data safety monitoring committee; Merck: advisory board; Oncogenix: data safety monitoring committee; sanofi-aventis: advisory board, consultant, grants. M. Hussain: Abbott: research grant; AstraZeneca: stockholder; Bristol-Myers Squibb: advisory board/consultant, research grant; Centocor: advisory board/consultant; Chiron: advisory board/consultant; Eli Lilly: advisory board/consultant; GlaxoSmithKline: stockholder; Johnson & Johnson: stockholder; Lilly: advisory board/consultant; Merck: research grant, stockholder; Novacea: advisory board/consultant; Pfizer: advisory board/consultant; sanofi-aventis: research grants; Wilex: research grant. P. W. Kantoff: Nothing to disclose. W. K. Kelly: Bristol-Myers Squibb: consultant, research support; Curagen: research support; Novartis: consultant; sanofi-aventis: consultant, research support. P. Mathew: Nothing to disclose. M. J. Morris: Agensys: research funding; Cytogen: research funding; sanofi-aventis: consultant. C. J. Ryan: Nothing to disclose. Howard M. Sandler: TAP: consulting. I. M. Thompson: Nothing to disclose.

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TEST KEY

1 d; 2 b; 3 e; 4 d; 5 a; 6 c; 7 e; 8 d
INSTRUCTIONS

- Refer to CME Information page “How to Obtain Credit”
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**Please circle the number that best represents your response to the following questions**

5 Strongly agree; 4 Agree; 3 Neither agree nor disagree; 2 Slightly disagree; 1 Disagree

This activity met its stated learning objective:

Discuss current recommendations for assessing and treating prostate cancer patients with low risk disease, intermediate/high risk disease, rising prostate specific antigen after local therapy and castration resistant disease

This CME activity was informative and well presented

I learned something that has changed my perspective

I learned something that may affect my practice behavior

I plan to change my practice as a result of something I learned from this activity

Please indicate any specific areas where you anticipate change to current practice (check all that apply)

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May we e-mail you to follow up on the value of this activity? YES NO
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I certify that I personally completed the activity Innovations and Challenges in Prostate Cancer based on the material presented. I request _______ [up to 2.0] AMA PRA Category 1 Credits™. Each physician should claim credit commensurate with the extent of his/her participation in the activity.

SIGNATURE ______________________ DATE ____________
CME SELF-ASSESSMENT TEST
2006 Conference on Innovations and Challenges in Prostate Cancer

Please circle one answer for each question. Self-correct using TEST KEY on bottom of CME Information page.

1. Which of the following agents are currently being investigated for prostate cancer prevention?
   a. vitamin E
   b. selenium
   c. finasteride
   d. all of the above
   e. none of the above

2. Which of the following is TRUE regarding patients with low-risk prostate cancer?
   a. Active surveillance increased sharply throughout the 1990s.
   b. There are significant trends toward lower risk at presentation.
   c. Rates of active surveillance have decreased since the start of this decade.
   d. A period of surveillance rather than immediate treatment is likely overused as a first management option.
   e. C and D

3. Which of the following is TRUE?
   a. All available therapies for prostate cancer may have a significant negative effect on patient health-related quality of life.
   b. As more men are diagnosed with curable tumors at younger ages, the course of the disease is lengthening.
   c. Risk assessment at the time of diagnosis based on available clinical data can help guide clinician-patient decision-making with respect to optimal treatment strategy.
   d. Patients with a PSA level less than 10 ng/mL, a biopsy Gleason score of 6, and a clinical stage of T1c or T2a have typically been classified as low risk.
   e. all of the above

4. Which of the following PSA values best indicates clinically significant, recurrent disease after surgery?
   a. 0.4 ng/ml confirmed on one occasion
   b. a PSA doubling time of >12 months
   c. 0.05-0.09 ng/mL
   d. a PSA doubling time of <6 months
   e. any detectable serum PSA

5. What is the only therapy proven to prolong survival of patients with castration-resistant metastatic disease?
   a. docetaxel
   b. disodium pamidronate
   c. ibandronic acid
   d. sodium clodronate
   e. zoledronic acid

6. What is currently considered the standard treatment option for men with taxane-resistant castration-resistant prostate cancer, owing to its role in pain palliation?
   a. thalidomide
   b. satraplatin
   c. mitoxantrone
   d. all of the above
   e. none of the above

7. Which of the following bone-directed therapies have demonstrated efficacy in reducing progression of metastatic disease?
   a. bisphosphonates
   b. radiopharmaceuticals
   c. RANK-ligand signal inhibitors
   d. all of the above
   e. none of the above

8. Which of the following vaccines are currently being assessed as immunotherapeutic agents for treating prostate cancer?
   a. Provenge
   b. GVAX
   c. Prostvac
   d. all of the above
   e. none of the above
Innovations and Challenges in Prostate Cancer: Summary Statement for the 6th Cambridge Conference


From the Lank Center for Genitourinary Oncology (PWK), Dana-Farber Cancer Institute (AVDA) and Department of Radiation Oncology, Brigham and Women's Hospital (AVDA), Boston, Massachusetts, Division of Hematology and Medical Oncology and Oregon Health and Science University Cancer Institute, Oregon Health and Science University (TMB), Portland, Oregon, Cancer Institute of New Jersey (RSDP), New Brunswick, New Jersey, Departments of Oncology and Urology, Johns Hopkins University (MAE), Baltimore, Maryland, Departments of Internal Medicine (Division of Hematology and Oncology) (MHAH) and Radiation Oncology and Urology (HMS), University of Michigan, Ann Arbor, Michigan, Department of Medical Oncology, Yale University (WKK), New Haven, Connecticut, M. D. Anderson Cancer Center (PM), Houston and Department of Urology, University of Texas Health Science Center at San Antonio (IMT), San Antonio, Texas, Genitourinary Oncology Service, Department of Medicine and Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center and Department of Medicine, Joan and Sanford E. Weill College of Medicine of Cornell University (MJJ), New York, New York, and Departments of Medicine (CJR) and Urology, Program in Urologic Oncology, Urologic Outcomes Research Group (PRC), University of California-San Francisco Comprehensive Cancer Center (CJR), University of California-San Francisco, San Francisco, California

Key Words: prostate, prostatic neoplasms, clinical conference [publication type]

The Sixth Cambridge Conference on Innovations and Challenges in Prostate Cancer, a symposium held in Cambridge, Massachusetts, October 30 and 31, 2006, was convened to review and discuss new data and recommendations related to prostate cancer. The forum addressed promising agents in development for treatment and prevention, and current approaches and recommendations for assessing and treating early stage disease as well as patients with biochemical failure (increasing PSA), castration resistant nonmetastatic, castration resistant metastatic and taxane refractory metastatic disease. The conference format combined brief presentations with extended periods of discussion. The conclusions and recommendations are summarized in this article and presented in more detail in the individual reports that follow.

CHEMOPREVENTION

Prostate cancer chemoprevention first attracted increased interest with the completion of the first phase III clinical trial, the Prostate Cancer Prevention Trial, reported in 2003 with more than 18,000 patients. The trial was closed early because of evidence that a decrease in prostate cancer risk was seen with the administration of finasteride. Although a significant reduction in cancers was seen, an increase in the number and proportion of tumors with Gleason scores of 7 to 10 led to initial concern with the use of the drug for this purpose. A recent analysis shed light on this paradox, finding that finasteride significantly improved the sensitivity of PSA and biopsy for overall cancer and high grade cancer. The results of ongoing studies will ultimately help guide us in making a recommendation regarding the use of 5α-reductase inhibitors as preventive agents. Vitamin E and selenium are now being assessed in an ongoing phase III study, the Selenium and Vitamin E Cancer Prevention Trial.

LOW RISK PROSTATE CANCER

Although curative therapy has been shown to decrease cancer specific and overall mortality for select men with prostate cancer, all available therapies may have a significant negative effect on patient health related quality of life. Furthermore, as more men are diagnosed with curable tumors at younger ages, the course of the disease is lengthening. Thus, patients and physicians must consider seriously the long-term implications of disease management decisions. Risk assessment at diagnosis based on available clinical data can help guide clinician-patient decision making with respect to the optimal treatment strategy. Patients with a PSA level of less than 10 ng/ml, a biopsy Gleason score of 6 and a clinical stage of T1c or T2a have typically been classified as low risk.

On a national level the use of active surveillance (watchful waiting) decreased sharply among patients at low risk throughout the 1990s, even as low risk tumors accounted for a steadily increasing proportion of diagnosed tumors. Current results show that the proportion of prostate cancer patients assigned to the low risk group as defined has stabilized at just less than half of patients with newly diagnosed prostate cancer in the first 6 years of the new millennium. However, in this group there are significant and ongoing trends toward lower risk at presentation. Rates of active surveillance in patients at low risk have increased since the start of this decade but, despite the ongoing downward trends in risk, a period of surveillance rather than immediate treatment is likely underused as a first management option for many such men. Standardized methods for surveillance are needed. Studies that critically assess optimal methods of followup (intervals of assessment, PSA kinetics, optimal use of biopsy, etc) and, moreover, methods for selecting out those appropriate for active surveillance using clinical and molecular markers are greatly needed.

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**INTERMEDIATE AND HIGH RISK PROSTATE CANCER**

The optimal treatment of intermediate and high risk prostate cancer is still debated. The subgroup of patients with a PSA level of greater than 10 ng/ml, a biopsy Gleason score of 7 or higher and clinical tumor category of T2b or T2c are at a higher risk for cancer specific death after standard treatment, suggesting that EBRT plus ADT or alternatively RP alone may be inadequate therapy for many men with such cancers. Patients with clinically organ confined disease may be considered for RP or high dose, well targeted radiation. Relapse rates can be significant and to our knowledge no evidence exists to date for combined modality treatment with surgery. Short-term ADT before surgery has not proved to be of clinical benefit. In contrast, dose escalation of EBRT appears to decrease relapse rates, although no evidence for a survival benefit yet exists. The addition of ADT to EBRT for patients at intermediate and high risk appears to be of benefit with respect to progression-free and overall survival in most studies. The optimal duration of this combination therapy is still under study. Whether higher doses of EBRT supplant the need for EBRT combined with ADT is not known. Chemotherapy has activity in those with prostate cancer but it is of uncertain clinical benefit. Ongoing trials are testing the role of chemotherapy in neoadjuvant and adjuvant settings with RP and radiotherapy.

**INCREASING PSA AFTER LOCAL THERAPY**

In patients with clinically localized prostate cancer who undergo focal treatment increasing serum PSA levels usually precede clinically detectable or metastatic disease by many years. Although many of these patients are unlikely to die of the disease, they may live with uncertainty and may be at risk for disease related morbidity.

In general increasing PSA values indicate recurrent disease after surgery. A PSADT that is short generally indicates clinically significant recurrence. A significant amount of work has been done in identifying relapsed patients at high risk for early metastases and prostate cancer specific mortality. PSA kinetics inform subsequent treatment strategies. Patients with low PSA values will have no detectable metastases. Local therapy after surgery, ie radiation, should be considered for select patients in the absence of metastases but the results are most satisfactory for those with later relapse and slowly increasing serum PSA levels, especially in those with positive surgical margins at initial surgery. The role of local salvage treatments for patients treated with primary radiation therapy has not been firmly established. Among the methods most often applied are surgery, cryotherapy and brachytherapy.

Patients with a Gleason score of 7 or less, who relapse after 2 years and who have PSADT longer than 10.0 months have a 3, 5 and 7-year probability of distant metastasis of 95%, 92% and 87%, respectively. Patients who have relapse before 2 years, have a Gleason score of greater than 7 and have PSADT shorter than 10.0 months have a 3, 5 and 7-year probability of distant metastasis of 54%, 30% and 21%, respectively. Although such patients are at higher risk for prostate cancer specific mortality, there is currently no consensus on the appropriate timing and form of systemic therapy for these patients. Thus, encouraging participation in clinical trials is essential to improving patient care.

The use of bisphosphonates in hormone naïve patients treated with ADT should be reserved for those with significant osteopenia or osteoporosis. No data are available to support their use as preventive agents against metastases and, moreover, long-term use may be associated with renal dysfunction, anemia and osteonecrosis of the jaw.

**CASTRATION RESISTANT DISEASE**

**Castration Resistant Nonmetastatic Disease**

In patients with an increasing PSA level after primary therapy a detectable PSA nadir is the earliest sign of impending androgen independent prostate cancer and a strong prognostic factor for death from prostate cancer. However, because of the low initial disease burden, the prognosis in these patients is better than the prognosis in patients with clinically advanced metastases.

Although a variety of therapies, eg secondary hormonal therapies, are used and are active for CRPC, adequately designed studies to detect a clinical benefit, ie a delay in the development of metastases or enhanced survival, have not been done. Ongoing randomized studies should enhance our understanding of the natural history of this disease state and future clinical trial design. One group reported that PSADT and PSA level predicted the time to clinical progression and, therefore, these baseline measures may be useful for selecting and/or stratifying patients in clinical trials. Clinical trials should be designed to include conventional study end points, such as time to clinical metastasis and survival. Such trials will provide the necessary information on the relationship between potential intermediate end points, such as PSA dynamics, other clinical and laboratory variables, and time to clinically evident metastasis and survival that can be used in clinical practice decisions and clinical trial design.

**Castration Resistant Metastatic Disease**

The only therapy that has proven to prolong survival in this clinical context is docetaxel based chemotherapy. Whether all patients should be treated up front with docetaxel as soon as they enter this clinical state remains uncertain. The consensus is that chemotherapy for patients with rapidly progressive or symptomatic disease should be initiated early. There is scant evidence that asymptomatic patients with slowly progressive or otherwise low risk disease are at any disadvantage by trying additional hormonal or investigational maneuvers before initiating chemotherapy. Patients who are candidates for chemotherapy should be registered for a variety of trials that are under way to test the value of adding other agents to docetaxel. The results of randomized trials are pending.

The use of bisphosphonates in this setting is based on 1 study that demonstrated a decrease in skeletal related events. The consensus of this group was that in the absence of a confirmatory study, the seemingly modest benefits associated with their use and the possibility of adverse effects, the indiscriminate use of bisphosphonates should be discouraged and further study identifying those most likely to benefit is needed. Moreover, the identification of more effective bone directed therapies is needed.
Taxane Refractory Prostate Cancer

In general CRPC is poorly controlled after resistance to front line chemotherapy with a time to progression of 3 months or less with second line therapy and a median survival of approximately 12 months. For patients presenting with taxane refractory disease it is appropriate to reassess disease progression, comorbidities, and palliative and therapeutic opportunities. This includes assessing whether a modified taxane regimen or reconsideration of secondary hormone deprivation is appropriate. For patients with small cell histological evolution studies have demonstrated a clinical effect with etoposide-cisplatin therapy.10

Mitoxantrone is currently considered a standard option for men with taxane resistant CRPC due to its pain palliation, although its activity is modest and there is no proven survival benefit. Combinations of taxanes and biologically active compounds are of considerable interest for treating CRPC and clinical studies in the second line setting are in progress. The results of a large, randomized study of satraplatin, an oral platin, as second line chemotherapy is pending analysis. Active agents must be identified. An alternate taxane or antitubular agent, or cyclophosphamide based therapy may be considered, although there is no evidence of a survival or quality of life benefit.11

PROMISING NEW AGENTS IN DEVELOPMENT

Several new therapeutic strategies are being evaluated to treat prostate cancer, including a variety of bone targeted agents, immunotherapeutic agents and novel targeted systemic agents. Bone metastasis occurs in the setting of a complex system of multiple interacting proteins and pathways that regulate the actions of osteoblasts, osteoclasts, the bone microenvironment and the growth of metastatic tumors. New insights into the pathways that affect bone growth and remodeling have led to the development of several therapeutic agents, which are being assessed as therapies for metastatic disease and bone loss, including bisphosphonates, radiopharmaceuticals, RANK ligand signal inhibitors and several others. As mentioned, commonly used agent zoledronic acid, a bisphosphate, has demonstrated a modest palliative effect but no antitumor activity or significant clinical benefit for prostate cancer in phase III randomized trials. Likewise radiopharmaceutical agents have shown some palliative effect but no clinical benefit for prostate cancer. It is recommended that future therapy development should be combination based, focusing on simultaneous targeting of multiple relevant pathways, most importantly the direct targeting of prostate cancer cells.

Immunotherapeutic agents attempt to use the immune response to block prostate cancer growth and kill residual cancers. Clinical trials are under way or being initiated for several vaccine approaches. APC8015 (Provenge®), a dendritic vaccine, has completed initial phase III testing in patients with hormone refractory prostate cancer. GVAX®, a tumor cell vaccine, is in phase III testing in patients with CRPC alone and in combination with docetaxel. Prostvac®, a poxvirus based vaccine, is also under study.

Several systemic agents are being investigated that target specific pathways in prostate cancer cell growth. Chief among them are cytotoxic agents, particularly microtubule inhibitors and agents that interfere with androgen signaling by reducing ligand or inhibiting signaling molecules. Candidates in development include heat shock protein 90 inhibitors and histone deactylase inhibitors. Another important pathway under investigation is the IGF-1/PTEN signaling pathway, which has a role in activating Akt to target mTOR. Several candidates are being evaluated in the clinic, including IGF-1R antibodies, phosphoinositide-3 kinase, Akt and mTOR inhibitors. Several agents that target other pathways shown to be important for solid tumor growth include platelet-derived growth factor inhibitors, represented by bevacizumab, vascular endothelial growth factor signaling inhibitors, represented by sunitinib and sorafenib, and thalidomide and lenolid, which are thought to block angiogenesis.

RECOMMENDATIONS

Certain consensus recommendations were proposed by the conference faculty to advance prostate cancer research and disease management, and improve patient care. 1) Develop methods for identifying patients appropriate for active surveillance using clinical and molecular markers. 2) Perform clinical trials to test novel therapies as adjuvants to surgery or radiation with the objective of improving disease-free and overall survival in patients with intermediate and high risk disease. 3) Perform studies to better define the natural history of castration resistant disease, and develop and fully support informative clinical trial designs suited to this patient population. 4) Use combination strategies for future therapy development, focusing on simultaneous targeting of multiple relevant pathways. 5) Consider new opportunities to test efficacy using long-term treatment strategies, including the use of agents that modulate metabolic processes that may affect multiple pathways.

Abbreviations and Acronyms
ADT = androgen deprivation therapy
CRPC = castration resistant prostate cancer
EBRT = external beam radiation therapy
PSA = prostate specific antigen
PSADT = PSA doubling time
RP = radical prostatectomy

REFERENCES


Chemoprevention of Prostate Cancer: Agents and Study Designs

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Purpose: With the completion of the Prostate Cancer Prevention Trial and the ongoing performance of several additional large-scale prostate cancer prevention trials interest in this intervention has increased. We review promising agents for prostate cancer prevention, clinical trial designs and how these agents may be used clinically.

Materials and Methods: We reviewed current and completed randomized chemoprevention trials for prostate cancer as well as the most promising agents for which evidence suggests that a decreased prostate cancer risk may result from their use.

Results: Evidence suggests that lycopene, decreased dietary fat, antioxidants such as α-tocopherol and selenium, nonsteroidal anti-inflammatory drugs and selective estrogen receptor modulators such as toremifene and 5α-reductase inhibitors may prove useful for decreasing the risk of prostate cancer in a man. Ongoing studies are examining these agents in the 3 general scenarios of 1) general population studies (finasteride, α-tocopherol and selenium), 2) increased prostate specific antigen with negative biopsy (dutasteride) and 3) prostatic intraepithelial neoplasia (toremifene and selenium).

Conclusions: There are many agents that may decrease the risk of prostate cancer. It requires careful study of the agents in specific populations to determine whether risk is reduced, the magnitude of the risk reduction and the spectrum of side effects associated with the agent. Physicians caring for men entering the range of age of prostate cancer risk must be aware of these preventive opportunities.

Key Words: prostate, prostatic neoplasms, chemoprevention, antineoplastic agents, prevention and control

Chemoprevention of prostate cancer has become an increasingly important public health approach to this somewhat ubiquitous disease. The reasons are compelling, including 1) the increasing risk of diagnosis during the lifetime of a man, approaching 18% in 2006, 2) the approximate 60% contribution of exposure to risk of the disease (as much as 40% of the risk of the disease is estimated to be genetic), 3) the recognition that the majority of prostate cancer cases and deaths occur during the later years of the life of a man, suggesting that a delay in diagnosis by 1 or more years could substantially affect mortality, and 4) the cost and morbidity of current approaches based primarily on early detection and treatment, an approach that has not been demonstrated to decrease population morbidity and mortality from the disease.

Chemoprevention of prostate cancer, better termed disease risk reduction, has attracted increased interest with the completion of the first phase 3 clinical trial (the Prostate Cancer Prevention Trial) as well as the completion of accrual of several additional phase III studies, of which the results are pending at this time. Unlike many neoplasms, prostate cancer suffers from a growing and lengthy list of opportunities for prevention of the disease. Because of the substantial expense, number of patients required and time for phase III studies, it is extremely important that care be taken in the selection of agents for prevention studies. To better understand these opportunities as well as the framework of clinical trials for their testing we reviewed some of the more promising agents as well as the clinical trial designs that are being used at this time for their evaluation. Due to space limitations the list of agents discussed cannot do justice to all agents and it is acknowledged that many important and promising agents are not included in this discussion.

PROMISING AGENTS FOR PROSTATE CANCER RISK REDUCTION

Lycopene
Lycopene is a carotenoid that is found in a variety of foods, including watermelon and tomato, and it has been found in epidemiological studies to be associated with a lower risk of prostate cancer. Study results are conflicting, some showing no risk reduction and others demonstrating a significant decrease in risk. Perhaps the most compelling of the positive analyses was from the Health Professionals Follow-Up Study, in which prostate cancer cases were ascertained in more than 47,000 subjects, ultimately identifying 2,481 men with prostate cancer. After examining lycopene intake the investigators found that lycopene intake was associated with a decreased risk of prostate cancer (RR 0.84, 95% CI 0.73–0.96, p = 0.003). Intake of tomato sauce, which was the primary source of this agent, was associated with a greater reduction of risk (RR = 0.77, CI 0.66–0.90, p <0.001) and an even greater reduction in risk for extraprostatic disease (RR 0.65, 95% CI 0.42–0.99). In the Prostate, Lung, Colorectal and Ovarian cancer study of the National Cancer Institute, a recent analysis of 1,338 prostate cancer cases, examining the intake of lycopene and tomato products showed some protective effect of intake in individuals with a family history of the disease but no overall protective effect of lycopene intake. Despite these unclear conclusions and no ongoing
phase III clinical trials many patients currently choose to ingest lycopene supplements, presumably to decrease the risk of disease.\textsuperscript{8}

**Dietary Intake of Red Meats and Fat**

An increased intake of animal fat and possibly red meat has been associated with an increased risk of prostate cancer.\textsuperscript{9} Because animal protein as a percent of protein intake is low in Asian countries, this observation has been suggested to account for differences in the risk of prostate cancer between Western and Asian countries, a risk that may be as great as 20-fold different.\textsuperscript{10,11} The cause of this association is unclear but postulated mechanisms include increased androgen levels with high fat diets as well as the weak estrogen activity of soy compounds in Asian diets.\textsuperscript{12,13} An intriguing recent observation in an animal model indicated that higher fat and caloric intake was associated with up-regulation of prostate 5α-reductase-2 gene expression.\textsuperscript{14} Although the evidence is intriguing, due to the complexity and other challenges (including adherence) of dietary interventions, it is unlikely that this intervention will ever be tested in adequately powered phase III trials.

**NSAIDs**

Preclinical evidence suggests that NSAIDs and cyclooxygenase-2 inhibitors cause apoptosis in prostate cancer cell lines.\textsuperscript{15} Several secondary analyses of other clinical trials, case-control and cohort analyses have suggested that NSAIDs may significantly decrease the risk of prostate cancer.\textsuperscript{16,17} Before the withdrawal of rofecoxib (Vioxx\textsuperscript{®}) from the market this agent was under study in a phase III prevention trial for prostate cancer. This study was subsequently closed. At this time due to the risk of cardiovascular disease with this class of agents it is unlikely that further studies will be performed.\textsuperscript{18}

**Selenium**

A growing body of evidence suggests that selenium may significantly reduce the risk of prostate cancer. Preclinical data suggest that this micronutrient, which is found in soil, incorporated into forage crops and, thereby, into animals, may decrease the risk of prostate cancer.\textsuperscript{19,20} How the agent causes this effect is unknown but a hypothesis is that by functioning as an essential cofactor for the enzyme glutathione peroxidase it may serve an antioxidant role.\textsuperscript{21} Epidemiological evidence also provides support for a global cancer prevention effect.\textsuperscript{22} In a phase III skin cancer prevention trial secondary analysis showed a 49% reduction in prostate cancer incidence in subjects receiving selenium.\textsuperscript{23} We have previously reported that oral selenium accumulates preferentially in the substance of the prostate.\textsuperscript{24} A current large-scale phase III study is currently ongoing to examine the impact of selenium on men with HGPIN with the hypothesis that the agent decreases the risk of subsequent diagnosis of prostate cancer.\textsuperscript{25}

**α-Tocopherol**

Evidence supporting α-tocopherol, one of the most biologically active of the tocopherols, as a potential preventive agent for prostate cancer substantially parallels that of selenium. 1) Preclinical data are supportive.\textsuperscript{26,27} 2) A possible mechanism of action is again through its role as an antioxidant, while it may also affect androgen concentrations.\textsuperscript{28,29} With a growing body of literature that inflammation may be related to prostate cancer carcinogenesis such a role may help explain its effect. 3) In a large-scale cancer prevention trial for lung cancer a 32% reduction in the risk of prostate cancer as well as in the risk of prostate cancer death was observed.\textsuperscript{30} Of concern for the use of α-tocopherol in a prevention setting is the finding of an increased risk of heart failure in patients at higher risk for cardiac disease.\textsuperscript{31}

**Toremifene**

Toremifene, a selective estrogen receptor modulator, has been found to decrease prevalent prostate cancers through nonandrogen pathways in a mouse model of prostate cancer.\textsuperscript{32} Currently approved for the management of breast cancer, toremifene was tested in a phase IIb trial for decreasing the prostate cancer risk in men with HGPIN.\textsuperscript{33} In this study 514 men with HGPIN were randomized to placebo, or 20, 40 or 60 mg toremifene daily. Although the 40 and 60 mg doses did not affect the risk of prostate cancer at 6 and 12 months, the 20 mg dose was associated with a 48% decrease in the risk of prostate cancer at 12 months. As a result of these promising data, a phase III trial is currently ongoing with this agent.

**Other Agents**

Two other agents (soy products and green tea) have a substantial lay following for their potential preventive activity. The chemical similarity of the group of isoflavones in soy to estrogenic substances has led to speculation that activity may be hormonally mediated.\textsuperscript{34} A combination of vitamin E, selenium and soy product is being investigated in a double-blind, placebo controlled, randomized study of men with HGPIN. This study has been funded since 2003 by the National Cancer Institute of Canada. Green tea is another agent that is widely thought to reduce the risk of cancer, perhaps through the high concentrations of polyphenols.\textsuperscript{35} An intriguing study from Italy that was reported in 2006 provided early results from an underpowered proof of principle study. A total of 60 men with HGPIN were randomized to green tea catechins vs placebo. One year after study initiation 1 of 30 patients treated with green tea was found to have prostate cancer compared to 9 of 30 placebo treated patients.\textsuperscript{36} These data should provide an impetus for larger studies with these agents.

**5α-Reductase Inhibitors**

In the early 1990s, as finasteride was approved for the treatment of lower urinary tract symptoms in men, it was initially thought that this disease process that affected more than half of aging men would lead to widespread use of the agent. Additionally, compelling evidence at that time suggested that intraprostatic androgens have a key role in prostatic carcinogenesis. Finasteride, due to its low risk of side effects and salutary effects on lower urinary tract symptoms as well as its significant reduction in the concentration of dihydrotestosterone (the primary intraprostatic androgen), was an attractive agent to modulate prostate cancer risk.

However, there are 2 isoenzymes of 5α-reductase. While in general there is an increase in the expression of 5α-reductase type 1 from benign prostatic hyperplasia to
HGPIN to prostate cancer, the expression of 5α-reductase type 2 also increases from HGPIN to prostate cancer.37 Two agents are currently in clinical use that inhibit these enzymes. Finasteride competitively inhibits the activity of the type 2 enzyme, while dutasteride affects types 1 and 2. In addition to preclinical data, a considerable volume of clinical data suggest that these agents can affect the risk of prostate cancer. For dutasteride a recent study in which men scheduled to undergo radical prostatectomy were treated with 3.5 or 0.5 mg of dutasteride or placebo showed that dutasteride treatment was associated with small tumor and prostate volumes but it did not effect tumor grade.38 Additionally, in a large-scale study of dutasteride for the treatment of lower urinary tract symptoms a significant reduction in prostate cancer risk was seen in the dutasteride group at 24 months (1.1% vs 1.9%) and at 27 months (1.2% vs 2.5%).39

The most compelling data supporting this class of agents for prostate cancer prevention arises from the Prostate Cancer Prevention Trial. Initiated in 1993 and reported in 2003, the study randomized 18,882 men with PSA less than 3.0 ng/ml and normal digital rectal examination to 5 mg finasteride per day or placebo. The study was closed 15 months before planned closure due to overwhelming evidence that the primary end point (prostate cancer prevalence) had been met. Ultimately a 24.8% reduction in prostate cancer risk was seen with finasteride.40 Although a significant decrease in overall cancers and especially Gleason 6 or less tumors was noted, an increase in the number and proportion of Gleason 7–10 tumors led to initial concern with the use of the drug for this purpose. Subsequent analyses have focused on potential study biases. Most cryptic of the observations was that men diagnosed early during the study due to increased PSA or abnormal DRE were more likely to be found to have high grade cancers, while those diagnosed after 7 years on study, after the greatest period exposed to the drug, had a similar rate of diagnosis of high grade disease. A recent analysis shed light on this paradox, showing that finasteride significantly improved the sensitivity of PSA for cancer overall and for high grade cancer.41 The results of ongoing studies will help further clarify the actual degree of change of high grade disease.

STUDY TRIAL DESIGNS

There is a range of potential study designs to explore the potential of these and other agents to reduce the risk of prostate cancer. It is a general consensus that it will be unlikely in the near future that clinical trials will explore the potential of these agents to decrease the risk of prostate cancer death in a man. Such a study would require as many as 100,000 subjects and as many as 2 decades to complete. It is for this reason that the prostate cancer incidence or prevalence is generally chosen for study. Given that a diagnosis of prostate cancer leads to many adverse consequences, including anxiety, cost, treatment complications, and the risk of recurrence and death from the disease, an intervention that could prevent this cascade of events would indeed be beneficial to society.

While phase III clinical trials (randomized and double-blind with clinically important study end points) are the mechanism by which clinical care is ultimately changed, earlier phase studies are important for planning these studies. We have previously described in detail the types of phase II studies that are useful for advancing the science of chemoprevention.42 Proof of principle phase IIA studies are the first of these types of studies. In these smaller studies putative chemopreventive agents are often examined that have a mechanism of action that can be evaluated in target tissues. An additional goal of these studies is to establish that the proposed agent achieves appropriate concentrations in the target tissue. A recent example of such a proof of principle study compared selenium administration vs observation before radical prostatectomy.43 In this study the goal was to measure the impact of selenium administration on serum, toenail and prostate tissues. A second preliminary trial design, the intermediate efficacy phase IIB trial, is to determine whether an agent modulates an intermediate end point biomarker. A challenge in prostate cancer is the paucity of validated intermediate end points (end points that are confirmed to be related to ultimate prostate cancer development). Reasonable such end points to study may include prostate intraepithelial neoplasia, angiogenesis and, the most commonly used end point, PSA. While these studies are commonly used to establish initial evidence of efficacy and occasionally to measure effect size (which would then allow for a better understanding of the sample size required for any subsequent studies), in the absence of validated intermediate end points 2 errors can occur due to the small sample size of these studies, that is detecting differences that ultimately prove to be less or absent, or finding no difference in the intermediate end point when there indeed is a difference in the ultimate risk of prostate cancer. Despite the challenges of these types of studies, given the expense, size and time required for phase III studies, it is becoming essential to have these data before proceeding to phase III studies.

Three designs have been used for current phase III clinical prostate cancer prevention trials. The Prostate Cancer Prevention Trial and SELECT opted to explore a prevention intervention in a general risk population. Each study accrued patients at low risk for prostate cancer, including PSA 3.0 ng/ml or less for PCPT, PSA 4.0 ng/ml or less for SELECT and normal DRE for the 2 studies. Because PCPT used an agent (finasteride) that affected PSA levels, it was necessary to adjust PSA on an annual basis. However, since it could not be determined whether some adjustment bias might artificially affect prostate biopsy differentially between the 2 arms, a 7-year end of study biopsy was scheduled. For SELECT because the 2 agents (selenium and vitamin E) do not affect PSA levels, community standard of care biopsy prompts are relied on for prostate biopsies after subject study enrollment.

The power of this study design is that the results are more generalizable to the general population. If it is anticipated that prevention activities would be most likely initiated while a man is at low risk for prostate cancer, ie with PSA less than 4.0 ng/ml and normal DRE, the results of these studies would be applicable to the healthy, aging population, which currently has a low prostate cancer risk.

Two other study designs are currently enrolling or following patients in phase III trials. The Reduction by Dutasteride of Prostate Cancer Events clinical trial enrolled approximately 8,000 men who were at a generally greater risk for prostate cancer due to several levels of eligibility.43 Men 50 to 60 years old must have PSA between 2.5 and 10 ng/ml, while men 60 to 75 years old must have PSA between 3 and 10
ng/ml. All men must have had a negative prostate biopsy before study enrollment. The study randomized men to 0.5 mg dutasteride vs placebo and each man was scheduled for followup prostate biopsy at 2 and at 4 years. Using the same concept of enrollment of a higher risk population into a clinical prevention trial toremifene is currently being studied in a phase III trial comparing the 20 mg dose to placebo for men with HGPIN. More than 1,260 men were planned to be enrolled and enrollment was completed in May, 2006 with interanalyses in late 2007 or early 2008.

CONCLUSIONS

Perhaps in no other human neoplasm are there so many agents or strategies to reduce cancer risk than in prostate cancer. However, substantial challenges exist in the completion of properly designed and powered studies to validate their efficacy as well as in the prioritization of agents for testing. Obvious additional challenges are how to even consider combinations of agents because mechanisms of action may be additive or synergistic.

Long-term strategies should seriously consider new opportunities to test efficacy, including the use of agents that modulate metabolic processes that may affect multiple diseases. A prime example is inflammation. Inflammatory processes have been implicated in prostate cancer and in other neoplasms as well as in cardiovascular disease and other processes of aging. The natural extension of this proposal would be a phase III trial comparing an anti-inflammatory strategy vs standard of care while tracking multiple outcomes with time. The potential to use 1 strategy and lead to a reduction in multiple disease processes is extremely attractive from a public health perspective.

Abbreviations and Acronyms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DRE</td>
<td>digital rectal examination</td>
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<tr>
<td>HGPIN</td>
<td>high grade prostatic intraepithelial neoplasia</td>
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<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
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<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
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<tr>
<td>SELECT</td>
<td>Selenium and Vitamin E Cancer Prevention Trial</td>
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REFERENCES


Contemporary Trends in Low Risk Prostate Cancer: Risk Assessment and Treatment

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Purpose: We updated national risk trends in prostate cancer with a focus on low risk tumors, reexamined trends in primary treatment for low risk tumors and substratified patients at low risk based on pretreatment clinical data.

Materials and Methods: Data were abstracted from the CaPSURE™ registry. A total of 10,385 men were diagnosed between 1990 and 2006 with localized disease. Low risk was defined as prostate specific antigen 10 ng/ml or less, Gleason score 6 or less and clinical T stage 2a or less. Temporal trends were assessed for patient distribution among risk groups and in the low risk group for individual risk factors, Kattan nomogram prediction, Cancer of the Prostate Risk Assessment score and primary treatment. The ability of the Cancer of the Prostate Risk Assessment score to substratify low risk prostatectomy cases was evaluated with survival analysis.

Results: The proportion of low risk tumors in CaPSURE almost doubled from 27.5% in 1990 to 1994, to 46.4% in 2000 to 2001 but it has been relatively constant since then. A growing proportion of low risk tumors are cT1c and virtually all are Gleason score 6. Prostate specific antigen and the percent of positive biopsies decreased throughout the study period, as did the mean Cancer of the Prostate Risk Assessment score. The use of active surveillance increased from a nadir of 6.2% in 2000 to 2001, to 10.2% in 2004 to 2006. The use of prostatectomy also increased, whereas the use of androgen deprivation and radiation decreased. The likelihood of recurrence increased significantly with increasing Cancer of the Prostate Risk Assessment scores.

Conclusions: Patients at low risk can be further substratified to identify those at very low risk based on clinical variables. The use of surveillance is increasing but overtreatment remains a concern in these patients.

Key Words: prostate, prostatic neoplasms, risk factors, prognosis, questionnaires

With 218,890 new cases anticipated for 2007 prostate cancer accounts for almost 30% of all male cancers. A total of 27,050 men are expected to die of the disease this year, a mortality rate that is surpassed only by that of lung cancer, and yet this represents only a small fraction of the number of men who are diagnosed. Curative therapy has been shown to decrease prostate cancer specific and overall mortality for select men with the disease. However, all available treatments exert a potentially significant negative impact on patient health related quality of life. Furthermore, as more men are diagnosed at younger ages with curable tumors, the time course of the disease is growing ever longer. Men may expect to live many years after treatment or in some men without treatment and, thus, they must consider seriously the long-term implications of their disease management decisions. Risk assessment at diagnosis based on available clinical data can help guide clinician-patient decision making with respect to the optimal treatment strategy. Patients with PSA less than 10 ng/ml, a biopsy Gleason score of 6 or less and a clinical stage of T2a or less have typically been classified as low risk. A growing body of literature supports a role for a trial of active surveillance for carefully selected men with low risk tumors. However, we have previously found that on a national level the use of active surveillance (watchful waiting) decreased sharply in patients at low risk throughout the 1990s even as low risk tumors accounted for a steadily increasing proportion of diagnosed tumors. We performed the current study with the 3 goals of 1) to update our description of national trends in prostate cancer risk at presentation, 2) to examine whether any new trends in risk are associated with corresponding changes in treatment patterns and 3) to assess our ability to substratify patients in the low risk group using the recently validated University of California-San Francisco CAPRA score.

MATERIALS AND METHODS

CaPSURE is a longitudinal, observational database of men with biopsy proven prostate adenocarcinoma who were actively recruited from 31 academic and community based urology practices. CaPSURE is a longitudinal, observational database of men with biopsy proven prostate adenocarcinoma who were actively recruited from 31 academic and community based urology practices.
practices across the United States. All patients with prostate cancer are recruited consecutively by participating urologists, who report complete assessment and treatment data. Data on patients diagnosed with prostate cancer before 1995 but who were still followed by a urologist were initially entered into the database retrospectively, while for those in whom cancer was diagnosed since 1995, all data entry has been prospective. Completeness and accuracy of the data are ensured by random sample medical record review every 6 months. Additional details of the project methods and a description of the cohort sociodemographic characteristics have been reported previously.

As of July 15, 2006, 13,124 men had registered and consented in the CaPSURE database. A total of 451 men in whom cancer was diagnosed before 1990 were excluded, as were 501 with metastatic and/or locally advanced (clinical stage T3b or greater) disease. A total of 1,787 men (14.6%) with localized disease were missing PSA, clinical T stage (2002 system) and/or biopsy Gleason score data, and they were also excluded, leaving 10,385 for analysis. Patients at low risk were defined as described. Patients at intermediate risk were defined as those with a PSA of 10.1 to 20 ng/ml, a Gleason score of 7 and/or a clinical stage of T2b. Patients at high risk were those with a PSA level of more than 20 ng/ml, a Gleason score of 8 or greater and/or a clinical stage of T2c-3a.

Multivariable risk was further assessed with 2 well validated instruments. The first instrument was the original Kattan preoperative nomogram, which predicts the percent likelihood of biochemical recurrence-free survival 5 years after surgery via a relatively complex mathematical weighting of Gleason score, clinical T stage and a cubic spline transformation of PSA. Calculation of the score for large tumors diagnosed with a PSA value of less than 2 ng/ml and cT1a and T1b tumors combined accounted for approximately a doubling of the risk of biochemical recurrence after prostatectomy.

We analyzed temporal trends in patient distribution among the 3 risk groups with periods defined to produce relatively even numbers of patients in each group and focus attention on the current decade. In the low risk group we further analyzed trends in individual risk factors (PSA, Gleason score, T stage and PPB) and in aggregate risk, as assessed by the Kattan nomogram prediction and CAPRA scores. We also analyzed trends with time in primary treatment in patients at low risk. A total of 494 patients (4.8%) in the analytical data set were missing data on primary treatment. An additional 143 men (1.4%) had primary treatment recorded as other or none as opposed to active surveillance, which is coded in CaPSURE as watchful waiting, and they were also excluded from treatment analyses. Use of NADT with time was also examined among patients electing each form of local therapy. Because patients were unevenly distributed across the periods, the statistical significance of temporal trends in risk factors and diagnosis, and in primary treatment patterns was assessed using the Cuzick nonparametric test for trend.

Finally, we performed survival analysis on patients at low risk undergoing radical prostatectomy to predict the risk of recurrence (PSA level greater than 0.2 ng/ml on 2 occasions or any second treatment at least 6 months after surgery) stratified by CAPRA score. For this analysis patients receiving any neoadjuvant (before surgery) or adjuvant (treatment within 6 months of surgery) treatment were excluded, as were those with less than 6 months of followup or fewer than 2 postoperative PSA values available. For this subset of 1,769 men Kaplan-Meier plots were produced, and the log rank test and Cox proportional hazards regression were used to identify the significance of the CAPRA score as a predictor of biochemical recurrence. All analyses were performed using Stata™ for Macintosh®, version 9.

RESULTS

Of the 10,385 patients included in this analysis, 2,323 (41.6%), 2,761 (26.6%) and 3,301 (31.8%) had low, intermediate and high risk prostate cancer at diagnosis, respectively. Figure 1 shows trends in the distribution of patients among the risk groups. The proportion of patients at low risk almost doubled from 1990 to 1994 (27.5%) to 2000 to 2001 (46.4%) and remained relatively constant since. The greatest decrease was among patients at high risk, from 46.0% in 1990 to 1994, 29.1% in 2000 to 2001 and 25.1% in 2004 to 2006, whereas the proportion of patients at intermediate risk was relatively constant.

Figure 2 shows trends in each risk characteristic among the 4,323 patients at low risk. The proportion of patients at low risk with clinical stage T1c disease increased dramatically and continued to increase from 29.9% in 1990 to 1994, to 78.3% in 2004 to 2006. cT2a tumors were less prevalent, and cT1a and T1b tumors combined accounted for approximately 1% of tumors diagnosed between 2002 and 2006. In terms of biopsy Gleason grading, the number of low risk tumors scored as less than 6, ie with primary or secondary pattern 1 or 2, continued to decrease from 67.1% of tumors in the early 1990s to 3.0% in recent years. The proportion of tumors diagnosed with a PSA value of less than 2 ng/ml remained essentially constant during the last 10 years but low risk tumors were increasingly likely to be associated with PSA 2 to 6 ng/ml rather than 6 to 10 ng/ml. Mean PSA also decreased steadily during the last decade from 5.9 ng/ml in 1995 to 1999, to 5.1 ng/ml in 2004 to 2006. Finally, PPB also decreased from a mean of 41% in 1990 to 1994, to 23% in 2004 to 2006. Although the mean did not change since 2000, the frequency of tumors with 10% or less PPB contin-

Fig. 1. Trends in patient clinical risk stratification at diagnosis. Percent of men stratified to low, intermediate (Intermed.) and high risk groups in each year group. Numbers indicate aggregate total percent for each group in 1990 to 1994, 1995 to 1999, 2000 to 2001, 2002 to 2003 and 2004 to 2006. Trend toward more low and less high risk disease at diagnosis was significant (p <0.001).
ued to increase to more than a third of low risk tumors in 2004 to 2006.

To assess possible changes in risk in the low risk group we applied 2 multivariate instruments, the Kattan nomogram and the CAPRA score (table 1). The mean CAPRA score among patients at low risk decreased from 2.0 to 1.4 during the study period (p < 0.001). CAPRA scores 0 and 1 became more common, whereas scores 2 and 3 decreased in this group (p < 0.001). The mean Kattan predicted likelihood of 5-year biochemical recurrence-free survival also increased slightly from 90.2% to 90.8% during the study period (p < 0.001).

Table 2 shows trends in primary treatment selection among patients at low risk. The use of RP increased in the 2000s to almost 60% of patients at low risk. The use of brachytherapy appears to have peaked, increasing from 3.6% in the early 1990s to 19% in 2000 to 2001 and then decreasing to 13% in 2004 to 2006. The use of EBRT and primary ADT monotherapy decreased in recent years among patients at low risk, whereas active surveillance, which decreased from 14.8% in 1990 to 1994, to 6.2% in 2000 to 2001, increased since then to 10.2% in 2004 to 2006. There were no obvious trends in the use of multimodal local therapy (RP plus EBRT or brachytherapy plus EBRT), each of which remained uncommonly used among patients at low risk. Likewise, the use of NADT in association with RP, cryotherapy and radiation therapy remained generally constant, decreasing slightly in the most recent years. Approximately 5% of contemporary patients with RP, and 30% of those with cryotherapy and radiation received NADT before primary

### Table 1. CAPRA and Kattan score trends in patients at low risk

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treatment. The overall trend in primary treatment selection was statistically significant (p < 0.001).

Of patients at low risk 11.2% experienced disease recurrence at a median followup of 35.6 months. Figure 3 shows the results of survival analysis. The log rank test demonstrated statistically significant differences in survival by CAPRA score overall (p < 0.001). Pairwise log rank comparisons revealed significant differences between CAPRA scores 3 and 2 (p = 0.002) and between scores 2 and 1 (p = 0.028) but not between scores 1 and 0 (p = 0.584). On Cox proportional hazards analysis each increase in CAPRA score above 0 was associated with a 1.7-fold risk of recurrence (95% CI, 1.39–2.06, table 3). Five-year actuarial biochemical recurrence-free survival varied in the low risk group from 93.7% for a CAPRA score of 0 to 63.3% for a CAPRA score of 3 and 33.6% for CAPRA scores of 4 to 6.

DISCUSSION

We previously reported a sharp increase in the proportion of prostate tumors diagnosed with low risk features during the CaPSURE project up to 2001.9 This trend has not continued during this decade to date. The distribution of tumors has remained relatively constant across the 3 risk strata since the prior analysis. On the other hand, in the low risk group there are significant, ongoing trends toward lower risk characteristics. Nonpalpable T1c tumors account for an ever growing proportion of low risk tumors, up to 78% from 30% across the study period. T1c tumors are associated with a lower risk of recurrence than T2a tumors under the Kattan nomogram12 but not under the CAPRA scoring system.10 T1a/b tumors detected by transurethral resection for presumed benign disease account for a negligible proportion of contemporary tumors.

Biopsy specimens assigned a Gleason score below 6 likewise accounted for only 3% of low risk tumors in 2004 to 2006, consistent with well documented changes in pathologist practices.15 Of note, however, a few tumors were assigned a primary or secondary Gleason pattern of 2 even in 2006. The mean PSA value among low risk tumors continues to decrease with tumors increasingly likely to be diagnosed with PSA 2 to 6 ng/ml rather than 6 to 10 ng/ml. Those diagnosed with a PSA value of less than 2 ng/ml represent a relatively constant fraction. A total of 68.8% of tumors were palpable T2a tumors diagnosed by abnormal digital rectal examination results and 9.9% were T1a/b. The remaining 21.3% were T1c. It is unclear what prompted biopsy among these patients, perhaps a strong family history, rapid PSA velocity or abnormal digital rectal examination results on the contralateral side from the positive biopsy specimen, coded appropriately by the diagnosing urologist as T1c.

The trends in stage and Gleason grade represent the continuation of trends that we previously reported, 9

| Table 2. Primary treatment trends in patients at low risk |
|---------------------|-----------|-----------|-----------|-----------|-----------|---------------|
| RP                  | 211 (53.7)| 377 (54.1)| 560 (52.5)| 637 (58.6)| 437 (59.6)| 2,222 (55.9)  |
| NADT                | (2.4)     | (6.1)     | (3.0)     | (4.6)     | (5.7)     | (4.5)         |
| RP + EBRT           | 11 (2.8)  | 14 (2.0)  | 5 (0.6)   | 3 (0.4)   | 39 (5.0)  | 75 (31.1)    |
| Cryotherapy         | 26 (6.6)  | 15 (2.2)  | 21 (2.0)  | 28 (2.6)  | 32 (4.4)  | 122 (3.1)    |
| NADT                | (15.4)    | (33.3)    | (38.1)    | (46.4)    | (25.0)    | (31.1)       |
| Brachytherapy       | 14 (3.8)  | 97 (13.9) | 207 (19.4)| 183 (16.8)| 95 (13.0) | 596 (15.0)   |
| NADT                | (14.3)    | (28.9)    | (32.4)    | (35.5)    | (29.5)    | (31.9)       |
| Brachytherapy + EBRT| 1 (0.3)   | 8 (1.2)   | 9 (0.8)   | 10 (0.9)  | 4 (0.6)   | 32 (0.8)     |
| NADT                | (0.0)     | (62.5)    | (55.6)    | (40.0)    | (25.0)    | (46.9)       |
| EBRT                | 51 (13.0) | 66 (9.5)  | 84 (7.9)  | 45 (4.1)  | 39 (5.3)  | 285 (7.2)    |
| NADT                | (11.8)    | (27.3)    | (45.2)    | (28.7)    | (23.1)    | (29.1)       |
| ADT                 | 21 (5.3)  | 47 (6.7)  | 113 (10.6)| 85 (7.8)  | 48 (6.6)  | 314 (7.9)    |
| Active surveillance | 58 (14.8) | 73 (10.5) | 66 (6.2)  | 94 (8.7)  | 75 (10.2) | 366 (9.2)    |
| Total No.           | 393       | 697       | 1,066     | 1,087     | 733       | 3,976        |
| NADT totals         | (5.4)     | (13.7)    | (15.2)    | (13.6)    | (11.6)    | (12.9)       |

Fig. 3. Kaplan-Meier curves for biochemical recurrence-free survival among patients with low risk prostate cancer undergoing radical prostatectomy, stratified by CAPRA score.

| Table 3. Survival analysis in patients at low risk by CAPRA score |
|---------------------|-----------|-----------|-----------|
| CAPRA Score | HR (95% CI)* | p Value |
| Continuous        | 1.70 (1.39–2.96) | <0.001 |
| 0                  | Referent | 69.7 (98.4–74.8) |
| 1                  | 1.51 (0.37–6.18) | 0.570 |
| 2                  | 2.26 (0.55–9.22) | 0.256 |
| 3                  | 4.31 (1.03–18.01) | 0.045 |
| 4–6                | 9.76 (1.82–58.40) | 0.013 |

* Continuous variable (4 to 6 treated as equal to 4) with each level compared with a CAPRA score of 0 as a referent.
whereas the prior study did not document a decrease in PSA levels between 1993 and 2001, perhaps due to a different categorization of PSA values (0 to 4 vs 4 to 10 ng/ml). Mean PSA was not assessed in the earlier study. The current analysis is the first to our knowledge to examine time trends in PPB rates. Mean PPB decreased by almost 50% during the 1990s and it has stabilized since the beginning of the new decade. However, there is an ongoing increase in the proportion of tumors diagnosed with 10% or less PPB, ie a single core of at least a 10-core biopsy. They now represent more than a third of low risk tumors, reflecting increased use of extended template biopsy techniques.16

Multivariate risk analyses yield further insights. The low risk group has been estimated to face an 85% likelihood of biochemical recurrence-free survival after RP.5 The preoperative Kattan nomogram predicted likelihood of 5-year recurrence-free survival for this group varied from 70% to 96%. In this series the mean Kattan predictions were essentially constant at approximately 90%. On the other hand, mean CAPRA scores decreased from 2.0 to 1.4 with tumors with CAPRA scores of 0 to 1, representing the patients at lowest risk, increasing from 26% to 60% of low risk tumors. We found that the CAPRA score was able to stratify patients treated with RP well in the low risk group. With increasing CAPRA scores the HR for recurrence progressed upward and 5-year actuarial survival decreased consistently.

A typical patient at low risk could be assigned a CAPRA score of up to 3 for age older than 50 years, PSA 6 to 10 ng/ml and/or a PPB of greater than 33%. A few patients in the low risk group had CAPRA scores of 4 to 6 because the traditional low risk group is defined by total Gleason score and, thus, it includes rare patients with Gleason 2 + 4 or 4 + 2 biopsy specimens. The survival results in this analysis for patients with CAPRA scores of 4 to 6 should not be taken as typical for all patients with RP with these scores, but they illustrate the point that the presence of Gleason pattern 4 disease drives outcomes and Gleason 2 + 4 or 4 + 2 tumors should not be included with patients at low risk in outcomes analyses.

With regard to treatment trends among patients at low risk, we previously reported a sharp decrease in use of active surveillance from 20.3% in 1993 to 1995, to 7.9% in 1999 to 2001, and raised concern regarding possible overtreatment among patients at low risk.9 A recent analysis from the population based SEER registries reached similar conclusions regarding the underuse of surveillance among patients at low risk, estimating overtreatment rates of 10% of patients with RP and 45% of those with radiation therapy in whom cancer was diagnosed in 2000 to 2002. Two important limitations of this study are that it considered patients at lower risk to be those with Gleason scores of 2 to 4 or those older than 70 years with Gleason scores of 5 to 7, an outdated classification of Gleason grading, and it included primary ADT with expectant management, which may not be valid in terms of cost, quality of life or outcomes.17

With increasing appreciation of the role of active surveillance for select patients with low risk tumors we now find a reversal of the trend, with active surveillance increasing from 6.2% of patients in 2000 to 2001, to 10.2% in 2005 to 2006. The use of brachytherapy decreased from a peak of 19.4% in 2000 to 2001, to 13.0% in 2005 to 2006, whereas the use of RP increased to almost 60% of patients at low risk. The use of primary ADT and NADT decreased from peaks of 10.6% and 15.2% in 2000 to 2001, to 6.6% and 11.6%, respectively, also marking a reversal of trends previously documented in CaPSURE and SEER.9,18

This study has limitations. Data are submitted only by patients and urologists. Therefore, any treatments by other practitioners that are not reported by patients to their urologists or in their questionnaires may be missed. Quality assurance mechanisms, including medical record review of all hospital admissions, help minimize this problem. An enrollment bias may persist that could artificially lower the proportion of patients on observation, that is patients who are diagnosed with prostate cancer but who elect not to undergo treatment may simply monitor their PSA levels with their primary care provider or not at all. However, if diagnosed with prostate cancer by a CaPSURE urologist and enrolled in the database, patients should have completed at least 1 treatment questionnaire.

CaPSURE practice sites have not been chosen at random and, thus, they do not constitute a statistically valid sample of the United States patient population. However, they represent a broad range of geographic locales, and a mix of academic and community sites, which we believe to be the best available sample for the analysis of temporal trends in “real world” practice. It is possible that the results would have been different with different grouping of the years of diagnosis but, given the consistently strong trends and low p values realized, this seems unlikely. The 1998 Kattan preoperative nomogram was recently updated by Stephenson et al.19 and the 2006 version incorporates more detailed information on the number of biopsy cores taken and positive. It is quite possible that the 2006 nomogram would better reflect a decrease in risk in the low risk group and would be more relevant to contemporary patients. However, the newer nomogram has not yet been validated in the community setting and it cannot readily be calculated for large numbers of patients. The CAPRA score has to date been validated only for patients undergoing RP and the results of our survival analysis should not yet be extrapolated to patients undergoing other treatments.

CONCLUSIONS

The proportion of prostate cancer patients assigned to the low risk group, as defined by a PSA level of 10 ng/ml or less, clinical stage Ta or less and a Gleason score of 6 or less, has stabilized at less than half of patients with newly diagnosed prostate cancer in the first 6 years of the new millennium. However, in this group there are significant and ongoing trends toward lower risk at presentation, as assessed by PSA, PPB and the multivariable CAPRA score. The CAPRA score is further able to stratify patients undergoing RP effectively in the low risk group based on the risk of biochemical recurrence, and helps confirm that patients with Gleason scores of 2 + 4 or 4 + 2 should not be considered low risk despite a Gleason sum of 6. Rates of active surveillance have increased since the start of this decade but, especially given the ongoing downward trends in risk, a period of surveillance rather than immediate treatment is still likely underused as a first treatment option for many eligible men with low risk disease. Methods for selecting those appropriate for active surveillance using clinical markers and molecular markers are greatly needed.
Abbreviations and Acronyms

ADT = androgen deprivation therapy
CAPRA = Cancer of the Prostate Risk Assessment
EBRT = external beam radiation therapy
NADT = neoadjuvant ADT
PPB = percent of positive biopsy cores
PSA = prostate specific antigen
RP = radical prostatectomy
SEER = Surveillance, Epidemiology and End Results

REFERENCES


Assessing and Treating Patients With Increasing Prostate Specific Antigen Following Radical Prostatectomy

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Purpose: In patients who undergo local treatment for clinically localized prostate cancer evidence of increasing serum prostate specific antigen usually antedates the development of clinically evident metastasis by many years. Prostate specific antigen is used to guide subsequent salvage strategies, such as postoperative radiotherapy, androgen ablation or active surveillance with delayed intervention. We discuss options for management in patients who have increasing prostate specific antigen after radical prostatectomy.

Materials and Methods: The current status of treatment approaches was reviewed to provide an update on frequently used management strategies.

Results: Increasing prostate specific antigen values of 0.2 to 0.4 ng/ml are used to indicate recurrent disease after surgery. Restaging is recommended to determine whether metastatic disease can be detected, although many patients with low prostate specific antigen values will have no detectable metastases. Local therapy should be used for select patients in the absence of metastases but the results are most satisfactory for relatively slowly increasing prostate specific antigen with values below 1.0 ng/ml and lower Gleason score neoplasms because these tumors are more likely to have localized recurrences.

Conclusions: Current knowledge about patients with biochemical relapse after radical prostatectomy is primarily related to their natural history. Although approximately 70% of these patients are unlikely to die of the disease, they remain at risk for the development of metastasis and disease related morbidity. Currently no general consensus exists regarding standard systemic treatment approaches for these patients and inclusion in clinical trials remains the most important priority.

Key Words: prostatic neoplasms, radiotherapy, prostatic-specific antigen; prostate

Almost 2 decades have evolved since the introduction of PSA as a routine management tool for patients with prostate cancer. Its application has profoundly influenced virtually all aspects of the disease. In patients who undergo local treatment for clinically localized disease evidence of increasing serum PSA levels usually antedates the development of clinically evident metastasis by many years. PSA is used to guide subsequent salvage strategies, such as postoperative RT, androgen ablation or active surveillance with delayed intervention. Although postoperative RT is widely used for biochemical recurrence, no clear-cut consensus exists on what constitutes appropriate standards of care with regard to systemic management. Despite the lack of evidence based data to support any approach urological oncologists (medical and radiation oncologists, and urologists) generally make therapeutic recommendations in response to inherent patient concerns about the prospect of the morbidity and mortality caused by the disease.

INCREASING PSA AFTER SURGERY

Surgery is a commonly used modality in the initial management of localized prostate cancer. In the Surveillance, Epidemiology and End Results database from 2000 to 2002 patients 65 years or younger with moderately to poorly differentiated prostate cancer (Gleason score 5 or greater) underwent RP 55% of the time with the remainder divided between RT and watchful waiting. Data from large series indicate that approximately 20% to 50% of patients who undergo RP will have biochemical relapse, and so the management of this scenario (increasing PSA after RP) is unexceptional.2,3

DEFINITION OF PSA FAILURE AND RE斯塔TING

The exact PSA threshold for defining postoperative biochemical failure has not been completely characterized. The use of supersensitive PSA assays is not widespread because of the concern for false-positive indications of tumor recurrence. Amling et al reviewed the records of patients to see what postoperative PSA threshold led to subsequent PSA failure (3 consecutive increases) implying definite active tumor recurrence, and suggested that a PSA of 0.4 ng/ml should be the minimum value for defining recurrence to avoid the use of unnecessary salvage therapies.4 Nevertheless, increasing postoperative serum PSA levels above 0.2 ng/ml in general are considered to represent evidence of relapse. However, a
small proportion of patients, usually with favorable clinical and pathological features, remain with stable and low below 0.4 ng/ml detectable serum PSA levels of undefined clinical significance. A threshold value of 0.4 ng/ml represented the best fit in a multivariate Cox model criteria that used clinically distant metastasis as the end point. In a recent report by the PSA Working Group a value of 0.4 ng/ml was the recommended value to define relapse on clinical trials. However, clinical trials that investigate the use of postoperative salvage therapies have frequently used lower thresholds than 0.4 ng/ml, such as greater than 0.2 ng/ml.

When patients have biochemical failure, regardless of the threshold there is often an attempt to determine the location of the disease. Digital rectal examination to detect palpable recurrences, bone scan and axial pelvic imaging, such as computerized tomography or magnetic resonance imaging, are used, although the probability of positive findings is low unless PSA is at least 5 ng/ml. Other imaging studies are also occasionally used. This staging reevaluation is most pertinent when additional local treatment, such as prostate fossa RT, is under consideration since the presence of distant metastatic disease completely mitigates against the benefit of local treatment. At this time no evidence based consensus exists on appropriate definition of PSA levels to be used as the threshold to perform systematic evaluations. However, a proportion of patients with low PSA have unexpectedly demonstrated evidence of positive findings on bone scans, which ultimately proved to be evidence of metastatic disease. Sequential evaluation of bone scans and computerized tomography can provide useful information in cases of equivocal, nonspecific findings when metastatic disease cannot be excluded and it may prevent the need for invasive diagnostic procedures.

LOCAL VS DISTANT RECURRENCE

As noted, current tests provide little help to determine which patients experience disease recurrence locally after RP. The determination of which patients are likely to have local disease and who are candidates for local salvage radiation is usually based on clinical and pathological parameters, and PSA dynamics. Partin et al reported an algorithm that may assist in the estimation of the probability of local relapse. In their report of a single institutional experience they found that the probability of local relapse was inversely proportional to Gleason score, pathological stage, serum PSA at 1 and 2 years, and PSA velocity. Typically patients with local relapses who were more likely to respond to salvage local radiation had a longer time to PSA relapse (2 years or longer), Gleason scores 7 or less, organ confined disease and PSA velocity shorter than 0.75 ng/ml per year based on serum PSA determinations at every 3-month interval. Stephenson et al reported that the probability of effective salvage postoperative radiation was associated with Gleason score 7 or less, PSADT longer than 10 months and the presence of positive surgical margins in patients with otherwise organ confined disease.

NATURAL HISTORY OF PATIENTS WITH BIOCHEMICAL RECURRENCE AFTER RP

In 1999 Pound et al reported data on 1,997 patients who underwent RP at Johns Hopkins University. This report involved patients who demonstrated evidence of increasing serum PSA (0.2 ng/ml or greater) after RP performed by 1 surgeon (Dr. P. C. Walsh) and who did not receive hormonal therapy until metastatic disease became evident. Factors that predicted the probability of distant metastasis on multivariate analysis included surgical Gleason score, time to biochemical relapse and PSADT. Table 1 and figure 1 show the updated data. Patients who had a Gleason score of 7 or less, relapse after 2 years and PSADT longer than 10.8 months had a 3, 5 and 7-year probability of distant metastasis of 95%, 92% and 87%, respectively (table 1). Patients with relapse before 2 years, Gleason score greater than 7 and PSADT shorter than 10.8 months had a 3, 5 and 7-year probability of distant metastasis of 54%, 30% and 21%, respectively. A subsequent report by Eisenberger et al indicated that PSADT was clearly the most powerful predictor compared with the other parameters. Figure 2 shows this by depicting the Kaplan-Meier distribution of distant metastasis in the groups of patients with Gleason scores 5 to 7 vs 8 to 10 according to a PSADT of 10 months or more, or less than 10 months.

Freedland et al reported the probability of PCSM on the same Johns Hopkins University database. Again, in this report surgical Gleason score, time to biochemical relapse and PSADT were the significant predictors. Figure 3 shows Kaplan-Meier prostate cancer specific survival curves for patients with the most predictive PSADT cutoff values in the multivariate analyses model. D’Amico et al assessed survival distributions in a large group of patients with evidence of biochemical recurrence after surgery or radiation and stressed the association, especially in the subset with a PSADT of 3 months or less, which represented only a small proportion of patients in the entire population. Their observations are similar to the Johns Hopkins experience, which also indicates that patients with short PSADT have a high likelihood of dying of metastatic prostate cancer. However, they represent only approximately 6% of the population with PSA relapse. Table 2 shows the estimates of PCSM in the Johns Hopkins University experience.

CURRENT PRACTICE AND RESULTS

Current practice for patients with biochemical failure after RP has been studied by the Cancer of the Prostate Strategic Urological Research Endeavor investigators. Of 303 patients with increasing PSA levels (at least 2 values of 0.2 ng/ml or greater) after RP by 36 months after biochemical failure, surprisingly only 44% had received any subsequent

<table>
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<th>Table 1. Probability of distant metastasis after RP</th>
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<td><strong>Gleason Score</strong></td>
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Cox model of Gleason score, recurrence year and PSADT.
therapy. In those who received secondary treatment it was approximately equally divided between androgen deprivation and RT delivered to the prostatic fossa.

Often RT is considered to be the only curative modality that can potentially be used to achieve durable biochemical remission after surgical failure. However, there is some debate over the absolute magnitude and durability of the benefit. The largest experience in this area is a multicenter consortium database that explored the benefit of RT and the prognostic factors that divide patients into various outcome classes. Stephenson et al recently reported on 1,540 patients who received salvage RT between 1987 and 2005. All had a PSA of 0.2 ng/ml or greater, followed by another increase. No patients received adjuvant androgen deprivation therapy. The data set is mature with a median followup of 4.5 years. Subsequently post-RT failure was defined as a PSA of 0.2 ng/ml or higher above the nadir or the initiation of additional therapy. Overall the progression-free probability was 19% at 10 years of followup but this was highly dependent on the baseline pre-RT PSA level. Patients with PSA between 0.2 and 0.5 ng/ml had a 6-year progression-free probability of 48%, whereas patients who had a PSA of greater than 1.5 ng/ml only had an 18% progression-free probability at the same time point. Other important factors that favor a longer progression-free probability are positive margins at RP, suggesting residual local disease, a lower RP Gleason score and longer pre-RT PSADT. Overall these data as well as other, smaller studies demonstrate that with salvage RT 1) some patients have prolonged biochemical remissions that can be considered cures, 2) the benefit is strongly associated with lower pre-RT PSA, implying (since this is the prognostic factor that is under physician control) that early salvage RT is desirable and 3) the morbidity of salvage RT is low.

HORMONAL THERAPY ALONG WITH RT AND CLINICAL TRIALS

The role of androgen ablation in combination with definitive external beam RT is secure for patients with high volume, high risk prostate cancer. However, the role of androgen ablation in the salvage RT setting is unclear. A clinical trial that will likely have an important influence in defining the role of hormonal therapy and postoperative RT is completed and results are pending additional followup. Shipley is the principal investigator of RTOG 9601, a randomized, placebo controlled trial for patients with biochemical failure who were assigned to prostatic fossa irradiation (64.8 Gy in 1.8 Gy fractions) plus 150 mg bicalutamide every day for 2 years or prostatic fossa irradiation plus placebo every day for 2 years. The allowable entry PSA level was 0.2 to 4.0 ng/ml. The study opened in 1998 and closed in 2003. The primary end point is overall survival. Of the patients entered 85% had a PSA of less than 1.5 ng/ml, 75% had a positive margin and 12% had detectable PSA immediately after RP. It is hoped that at least preliminary biochemical results will be available in 2007.

An area of major uncertainty is the appropriateness of the prostatic fossa as the RT target. As noted, a high secondary failure rate occurs when postoperative salvage RT is used. Likely explanations for a given failure include 1) subclinical distant metastases, 2) an inability to sterilize disease in the prostatic fossa and 3) marginally nonirradiated prostate cancer outside of the prostatic fossa but within reach of a local RT portal. Since data indicate a benefit to pelvic RT for patients at higher risk who are treated definitively, the question of increasing the RT volume to ad-

![Fig. 1. Natural history of progression following PSA recurrence after RP.](image)

![Fig. 2. Kaplan-Maier distribution of distant metastasis in patients with Gleason score 5–7 vs 8–10 according to PSADT 10 months or greater, or less than 10 months.](image)

![Fig. 3. PCSM according to PSADT.](image)

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<th>Table 2: Estimated 10-year PCa specific survival</th>
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<td><strong>PSADT (mos)</strong></td>
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<td>Recurrence greater than 3 yrs postop:</td>
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dress the issue of marginally nonirradiated prostate cancer outside of the prostate fossa is under active planning and will be part of an RTOG clinical trial soon. RTOG 0534 will randomize patients with PSA 0.2 to 2.0 ng/ml to prostate fossa RT alone, prostatic fossa RT with short-term androgen ablation or pelvic and prostatic fossa RT along with short-term androgen ablation.

CONSIDERATIONS FOR SYSTEMIC TREATMENT APPROACHES

Currently no consensus exists on what represents the optimal approach for these patients. When possible, these patients should be referred and entered into clinical trials. The data on natural history described provide some guidance on the planning and selection of treatment. Obviously the considerations for implementing systemic treatment in patients within favorable subgroups (PSADT more than 9 months, Gleason score 7 or less and PSA recurrence at more than 3 years) differ substantially from those in the most unfavorable groups. In the former group long-term survival figures are encouraging and comparable to those in an age matched population without prostate cancer (fig. 3). This suggests that delaying the onset of distant metastasis may be a reasonable primary therapeutic goal. Given the usual asymptomatic condition of these patients and their excellent quality of life, treatment may be withheld until later and the choice of relatively nontoxic approaches, such as intermittent androgen deprivation, nonsuppressive endocrine approaches such as nonsteroidal antiandrogens or new anti-metastatic compounds, are certainly reasonable options. It is important to stress that even in these patients there are no evidence based guidelines to implement any treatment at this time.

Patients with a PSADT of less than 9 months are clearly at a much more significant risk for metastatic disease and PCSM, and the types of treatment approaches that should be considered are more aggressive than in the former group. Indeed, the Johns Hopkins experience suggest that the PCSM of patients with a PSADT of less than 3 months is comparable to the survival of patients with metastatic disease (fig. 1). Although the survival of the patients with newly developed metastatic disease in this series appears to be longer than the published data, Johns Hopkins patients were sequentially followed with annual bone scans and serum PSA, and the diagnosis of metastasis is likely to become evident much earlier when the disease burden is much lower and survival is longer. This lead time effect is obviously a major factor behind the long survival in this and other series, showing the survival rates of patients sequentially followed from the time of biochemical relapse after primary treatment.

CONCLUSIONS

Current knowledge about patients with biochemical relapse after RP is primarily related to their natural history. Evidence suggests that Gleason score, time to biochemical relapse and PSADT are strong predictors of outcome and the data available from surgical series provide information on the outcome of these patients. Although approximately 70% of these patients are unlikely to die of the disease, they remain at risk for the development of metastasis and disease related morbidity. Approximately 30% of patients have significant subclinical disease and they are likely to die of metastatic prostate cancer despite the use of salvage local RT. Currently no general consensus exists regarding standard systemic treatment approaches for these patients, who no longer have a curative local option. Inclusion in clinical trials that investigate systemic approaches remains the most important priority.

Abbreviations and Acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>PCSM</td>
<td>prostate cancer specific mortality</td>
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<td>PSA</td>
<td>prostate specific antigen</td>
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<td>PSADT</td>
<td>PSA doubling time</td>
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<td>RP</td>
<td>radical prostatectomy</td>
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<td>RT</td>
<td>radiotherapy</td>
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<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
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REFERENCES

Prostate Specific Antigen Only Androgen Independent Prostate Cancer: Natural History, Challenges in Management and Clinical Trial Design

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Purpose: There is no current standard of care for patients with nonmetastatic androgen independent prostate cancer, a condition defined by increasing serum prostate specific antigen despite anorchid testosterone levels and no radiographic evidence of metastases. A consensus panel was convened to review data and propose a strategy for trial design and prioritization.

Materials and Methods: Published literature on the natural history of nonmetastatic androgen independent prostate cancer was reviewed. A panel discussion was held, focusing on reviewing current and past trials, and the development of research priorities for patients in this disease state.

Results: Based on 1 report the natural history of nonmetastatic androgen independent prostate cancer is relatively long but heterogeneous. External validation of these published findings has not been performed. Clinical trial design in this setting is impeded by heterogeneity and lack of knowledge about the natural history, prolonged time to clinical end points, such as the development of metastases or death, and a lack of knowledge about how intermediate end points, eg the development of bone metastases, are related to the long-term outcome, eg survival. In clinical practice a reluctance to use therapies with substantial toxicity as well as a lack of outcome data on such patients leaves a vacuum in which there is no standard of care, although secondary hormonal manipulations are widely used.

Conclusions: Further research is needed to define the natural history of this disease state, educate patients and clinicians about its distinct natural history and develop informative clinical trial designs suited to this patient population.

Key Words: prostate; prostatic neoplasms; prostate-specific antigen; receptors, androgen

Prostate cancer is second only to lung cancer with respect to the number of lives it claims among American men.1 Deaths from prostate cancer are almost universally related to the disseminated disease, which is unresponsive to hormonal manipulation. The clinical spectrum of AIPC has evolved in parallel with the evolution of hormonal therapy. Adjuvant hormonal therapy was only recently shown to improve survival in patients with high risk, localized and regionally disseminated disease.2–4 The practice of PSA monitoring after therapy delivered with curative intent along with therapeutic enthusiasm led to the increased use of hormonal therapy in patients without radiographic evidence of metastases. For example, approximately a third of patients who have PSA relapse after radical prostatectomy are treated within 12 months of relapse and most of these patients receive hormonal therapy.5 Earlier use of hormonal therapy coupled with PSA as a therapeutic end point has generated a new form of AIPC, a condition characterized by increasing PSA in the presence of anorchid testosterone with no radiographic evidence of disease dissemination. We reviewed available data on the natural history and treatment of patients with nonmetastatic AIPC, and propose a strategy for trial design and prioritization.

Natural History of AIPC

Serum PSA response to hormonal therapy allows the early detection of androgen independent disease. Indeed, even before the PSA increase detectable levels of serum PSA can provide important prognostic information. In patients with increasing PSA after primary therapy a detectable PSA nadir is the earliest sign of the impending emergence of androgen independent disease and a strong prognostic factor for death from prostate cancer. Stewart et al reported that among 747 men those with a PSA nadir of above 0.2 ng/dl had 7-year prostate cancer specific mortality between 54% and 72% depending on pretreatment PSA doubling time.6 D’Amico et al also found that the PSA response to initial hormonal therapy was a predictor of prostate cancer specific mortality.7

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† Financial interest and/or other relationship with Novartis.
Because PSA-only AIPC is a new entity, relatively little is known about the natural history of this disease state. This lack of knowledge hampers patient treatment and clinical trial design. In the only article of its kind Smith et al described the natural history of 201 such patients who participated in a randomized, controlled trial of zoledronic acid but received placebo.\(^8\) It is instructive to consider that this trial, which was designed to measure time to first bone metastasis, was aborted because the rate of metastatic development was lower than expected. Overall 33% of patients had bone metastases within 2 years and median bone metastasis-free survival was 30 months. Baseline PSA more than 10 ng/ml and PSA velocity independently predicted shorter time to the first bone metastasis, and metastases-free and overall survival. Additional studies of this kind are needed to gain greater confidence in the generalizability of these data but it appears that the prognosis in men with PSA only AIPC is relatively good compared to the prognosis in those with AIPC and metastatic disease. Absolute PSA and the rate of increase can further refine prognosis and identify subgroups at higher risk for clinically metastatic disease.

BIOLOGY OF AIPC AND IMPLICATIONS FOR NOVEL THERAPY

The biological mechanisms underlying the development of androgen independent growth are diverse and only partly understood. Molecular profiling studies show that 1 biological feature that is highly conserved in the process of disease progression is continued signaling by AR.\(^9\,10\) A growing body of literature has demonstrated that AR axis activation in the androgen deprived microenvironment results from 1 or more of a number of events that include promiscuity of the receptor for alternative steroid ligands, possibly via missense mutations of AR and/or amplification of the AR gene,\(^11\) leading to hypersensitivity to low levels of ligand, transactivation by coactivators and direct activation by other pathways (insulin-like growth factor receptor, Her-2/neu and AKT).\(^12\) Furthermore, the finding that intratumor levels of androgen adversely affect prognosis suggests that androgen deprivation treatment may select for the outgrowth of tumors that are able to sequester or synthesize androgen and further support the role of AR in the growth of androgen independent disease.\(^13\) Although a detailed discussion of these mechanisms is beyond the scope of this review, the preponderance of the evidence suggests that persistent AR activity is a hallmark of prostate cancer progression. Because PSA expression is regulated by AR, the increasing PSA level in these patients provides clinical evidence that AR is active and provides support for the hypothesis that AR remains a critical target for the development of new therapies for this patient population.

CHALLENGES IN CLINICAL TRIAL DESIGN FOR PSA-ONLY AIPC

Clinical trial design in this patient population is hampered by a number of challenges. The natural history is not completely defined. The article by Smith et al stands alone in the literature\(^8\) and until the outcomes of other groups of patients are reported we will not know whether the report by Smith et al is representative and generalizable. Time to a clinically important event is long. Patients and physicians may be unwilling to observe an increasing PSA level without intervention even in the absence of clinical disease progression. Appropriate intermediate end points are not validated. Treatment induced PSA reduction in this setting is of unknown significance. Although PSA changes are not a surrogate for clinical benefit in metastatic AIPC, the use of PSA reduction as a tool to screen for drug activity is widely accepted and grounded in extensive data that demonstrate a correlation between treatment induced PSA reduction and survival.\(^14\) Such data are not available in this population and it is not known whether treatment induced PSA reduction is or is not associated with a delay in clinical disease progression. Treatment induced changes in the rate of PSA increase are of uncertain significance. Randomized studies in hormone naïve (noncastrate) patients with increasing PSA levels demonstrated a significant placebo effect on PSA slope.\(^15\) Such studies have not been completed in similar patients with AIPC and, thus, little is known about the potential of placebo to affect the slope of PSA in this setting or about the clinical significance of treatment induced changes in PSA slope. Even clinical end points have not been fully credentialled in this patient group. Although it is intuitively appealing, the link between the development of metastases and overall survival has not been studied, raising the question of whether delay in the development of metastases would be an appropriate regulatory end point for clinical trials in this patient population. Appendix 1 shows these challenges along with suggested solutions.

ONGOING CLINICAL TRIALS IN NONMETASTATIC HORMONE REFRACTORY PROSTATE CANCER

Clinical trials in the nonmetastatic AIPC disease setting have proved difficult and they face the further challenge of appropriately balancing the risk of therapy with the relatively indolent course of the disease and the absence of disease related symptoms. The failure of ECOG study 1899 to accrue patients serves as an example of this difficulty and is a cautionary note for investigators in this arena.

ECOG 1899 was a randomized, phase III, cooperative group study in the setting of nonmetastatic prostate cancer designed specifically to address the question of whether secondary hormonal therapy (ketoconazole) or chemotherapy with docetaxel was the most appropriate subsequent therapy after androgen withdrawal in patients with AIPC. Unfortunately despite careful design, rational attention to disease biology and high prioritization by a prominent cooperative group the trial failed to accrue sufficiently and closed in early 2005. The early termination of ECOG 1899 initially raised questions about physician and patient willingness to endorse randomization between cytotoxic chemotherapy and a nonchemotherapy treatment for asymptomatic disease
without established metastasis. However, this stands in contrast to the strong support for Southwest Oncology Group trial 9921, a trial of adjuvant chemotherapy for men at high risk that has accrued well and also targeted men without established metastases or cancer related symptoms. Currently several studies are under way or planned that test the efficacy of chemotherapy early in the clinical course of prostate cancer, suggesting that this modality may find use, if not in the adjuvant setting, in the lower disease burden of nonmetastatic AIPC.

With that said, in light of the experience of ECOG 1899, many large-scale clinical trials in this setting have centered on the use of nonchemotherapy approaches. One of the largest experiences to date in this setting used the oral agent atrasentan (ABT-627), an endothelin-A receptor antagonist. In a subset analysis of a randomized, phase II study of atrasentan vs placebo men with asymptomatic metastatic disease experienced a time to progression that was significantly longer than that seen in patients treated with placebo. Building on this, an ongoing phase III randomized study of atrasentan in the setting of nonmetastatic AIPC is under way. Having met its accrual goal of approximately 1,000 patients, data from the trial are expected within the next 1 to 2 years. In addition to the description of the effect of atrasentan in this setting, the placebo arm of this trial should teach us a great deal about the natural history of untreated disease and provide an opportunity to validate and extend the work by Smith et al.

In addition to this study, numerous phase I and II studies are under way in this setting (Appendix 2). Many such studies seek to determine the efficacy of novel secondary hormonal approaches and enhance the clinical responses to the inhibition of AR signaling. Combination studies have added to ketoconazole the bisphosphonate alendronate, the immunostimulatory cytokine granulocyte-macrophage colony-stimulating factor, and 5α-reductase inhibitor dutasteride. A novel agent, abiraterone acetate, which inhibits the 17α-hydroxylase/C17,20-lyase enzyme complex, is currently in phase II. By restricting inhibition to these enzymes it is hypothesized that adrenal insufficiency may not result, as is typically the case with ketoconazole. If fully developed, these therapies would represent a potential means of extending the period that prostate cancer is responsive to androgen deprivation therapy.

Other agents being studied in this arena include antiangiogenics such as the vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK/ZK 787, vitamin D analogues and growth factor inhibitors such as those in development targeting signaling in prostate cancer induced by insulin-like growth factor receptor.

The use of secondary hormonal manipulations in this setting has intuitive appeal because they target the 1 known mechanism of tumor growth, that is persistent AR mediated signaling. A currently unanswered question is whether the response proportion to such approaches differs between patients with and without metastases. Data from a phase II trial of ketoconazole plus the immunostimulatory cytokine granulocyte-macrophage colony-stimulating factor suggests that, although response proportions may not be different compared with those in the metastatic setting, time to progression in nonmetastatic cases may be significantly longer. This is consistent with a long natural history of this disease state, as supported by the data from Smith et al. Strictly speaking there may be no substantial difference in AR activity in patients with vs without metastasis, although definitive data in this regard are lacking. Further descriptive data and patient stratification along these lines may be useful in the selection of patients for future trials.

**RECOMMENDATIONS FOR ADVANCING CARE**

Although PSA-only AIPC is a difficult condition to study, it is also an important opportunity. This disease state is a dichotomy characterized by a substantial risk of cancer related death, even if delayed, in the setting of a low initial disease burden. Such patients are more likely to benefit from effective therapies than those with clinically evident metastases and a larger tumor burden, for whom longer term survival is unlikely. Thus, despite the design challenges PSA-only AIPC should be the subject of aggressive study of new agents. There are steps that should lead to improved care.

1) Further define the natural history of the disease to support clinical care decision making and facilitate clinical trial design. Available data sets should be analyzed, reported and, when needed, shared to rapidly grow our understanding of this disease state. 2) Pool available data from therapeutic studies to develop intermediate end points. Studies that measure PSA levels or other biological changes in response to therapeutic intervention and then gather followup data that include a clinically relevant event such as the development of metastases or death would be particularly valuable in exploratory analyses to determine whether such changes could be of value to screen for drug activity. 3) Examine available data to determine whether PSA slope is affected by placebo treatment and whether changes in PSA slope are associated with delay in clinical disease progression. 4) Increase our knowledge of the biology that underlies this disease state and apply that knowledge to select therapeutic targets and agents. 5) Educate patients and physicians about the natural history of this condition and encourage them to support clinical trials. 6) Develop informative clinical trial designs and refine them as we learn more about the natural history of this disease. Among the most important decisions in this regard is the selection of appropriate clinical trial end points in this setting. Insofar as the relationship between changes in PSA kinetics and clinical benefit is unknown, trials should focus on clinical end points such as time to the development of metastases and overall survival. Furthermore, clinical trial end points should be sought that correspond not only to the clinical well-being of the patient, but also to the biological mechanisms targeted by the agent. For example, PSA end points may be appropriate for a novel antiandrogen but not for an anti-integrin treatment such as cilengitide, whose properties may be reflected more in a delay in metastases. 7) Fully characterize the pattern of initial metastases and examine the relationship between initial clinical end points, ie the development of skeletal, nodal or visceral metastases, and overall survival.
APPENDIX 1

<table>
<thead>
<tr>
<th>Challenge and Possible Solutions in Clinical Trial Design in AIPC</th>
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<tr>
<td><strong>Problem</strong></td>
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<tr>
<td>Natural history is not completely defined.</td>
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<tr>
<td>Time to a clinically important event is long.</td>
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<tr>
<td>Risk of clinical disease progression is heterogeneous.</td>
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<tr>
<td>Patients and physicians may be unwilling to observe a rising PSA without intervention.</td>
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<tr>
<td>Treatment induced PSA reduction in this setting is of unknown significance.</td>
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<tr>
<td>Treatment induced changes in the rate of PSA rise are of uncertain significance.</td>
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<tr>
<td>The relationship between the development of metastases and death is not well characterized.</td>
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APPENDIX 2

<table>
<thead>
<tr>
<th>Ongoing Clinical Trials in the United States of Patients With Nonmetastatic AIPC</th>
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<tbody>
<tr>
<td><strong>Target</strong></td>
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<td>Epidermal growth factor receptor</td>
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<td>Integrin</td>
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<tr>
<td>Vascular endothelial growth factor receptor</td>
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<tr>
<td>Rank-Rank-L</td>
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<td>Adrenal androgens</td>
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</tbody>
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Source: www.clinicaltrials.gov.

Abbreviations and Acronyms

- **AIPC** = androgen independent prostate cancer
- **AR** = androgen receptor
- **ECOG** = Eastern Cooperative Oncology Group
- **PSA** = prostate specific antigen

REFERENCES


Castration Resistant, Taxane Naïve Metastatic Prostate Cancer: Current Clinical Approaches and Future Directions

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From the Genitourinary Oncology Service, Department of Medicine, and Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center (GAG, MJM) and Department of Medicine, Joan and Sanford E. Weill College of Medicine of Cornell University (GAG, MJM), New York, New York, and Departments of Medicine and Urology, University of Michigan Comprehensive Cancer Center (MH), Ann Arbor, Michigan

Purpose: With the wide use of prostate specific antigen to detect response and disease progression resistance to androgen deprivation is being detected at an increasingly earlier stage. We focused on the current management and novel investigational strategies for the chemo naive patient population with castration resistant metastatic disease.

Materials and Methods: We reviewed standard and investigational hormonal, chemotherapeutic, biological and immune based strategies for patients with castration resistant metastatic prostate cancer who have not yet received taxane based chemotherapy.

Results: Our understanding of the natural history of this group of patients is evolving. A variety of standard and experimental treatment options are available for this group of patients. Manipulating the androgen receptor signaling axis, targeting antiangiogenic strategies, harnessing the immune system and optimizing docetaxel based regimens and novel cytotoxic agents are under investigation.

Conclusions: Multiple agents currently under development offer a promise of palliation and prolongation of survival above and beyond that of docetaxel. In the absence of guidance from randomized trials with regard to chemotherapy timing, and considering the modest effects of docetaxel on survival, decisions regarding choice of therapy (standard chemotherapy or experimental therapies) must be based on careful consideration of the functional status of each individual, presence of symptoms, comorbidities and overall therapeutic objectives.

Key Words: prostate; prostatic neoplasms; drug therapy; immunotherapy; receptors, androgen

Historically patients with prostate cancer with metastatic disease that progressed through androgen deprivation had no available therapy that could prolong survival. Such patients were faced with the prospect of progressive bone pain, neurological compromise and diminished quality of life before dying of disease. The outlook for these patients improved when 2 large, randomized, prospective trials, TAX327 and Southwest Oncology Group 99-16, involving more than 1,700 patients, compared docetaxel based therapy with mitoxantrone and prednisone, and demonstrated a 20% to 25% improvement in overall survival in favor of the taxane containing arms as well as improved pain control and quality of life.1,2

The use of PSA has resulted in a significant stage migration even in the setting of castration resistant metastatic disease, such that a significant proportion of these men are asymptomatic despite a PSA increase or objective progression on imaging (see figure). Coupled with the availability of effective chemotherapy this poses a dilemma for patients and their treating physicians, specifically with regard to the timing of systemic therapy. This dilemma is based on the desire to maintain quality of life while minimizing cancer related morbidity. In addition, it is clear that, while docetaxel is effective, this efficacy is modest and better therapies are definitely needed.

We addressed the spectrum of therapeutic options that are available for asymptomatic, docetaxel naïve patients with metastatic castration resistant prostate cancer. The options include standard second line hormones, standard docetaxel, investigational therapy alone and investigational therapy with docetaxel.

RISK ASSESSMENT AND THERAPEUTIC DECISION MAKING

Although metastatic castration resistant prostate cancer is the terminal stage of disease for virtually all patients, the natural history is variable among patients. Thus, clinical trial design and clinical decision making for an individual must consider individual risks. Two models specifically address the risk of dying in the general castrate metastatic patient population, including 1 by the group at Memorial Sloan-Kettering Cancer Center and 1 by Cancer and Leukemia Group B.3,4 However, neither of them distinguish between patients who have not yet received docetaxel based chemotherapy and those who are refractory to it, and the 2 nomograms are based on patients with significantly ad-

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With a variable natural history and lack of guidance based on clinical trials with regard to the optimal timing of chemotherapy most clinicians would believe that a patient with rapidly progressive or symptomatic disease warrants treatment that has a likelihood of more rapid action and in this regard taxane based therapy would be implemented. Indeed, TAX-327 demonstrated that symptoms can be effectively palliated using docetaxel and such effects may independently predict survival. However, to our knowledge it is not known whether patients who are asymptomatic or who have lesser burdens of disease benefit similarly or more. Such patients represent a unique treatment opportunity because their clinical situation does not necessarily demand immediate application of chemotherapy. Such patients and their physicians might elect to explore investigational biological strategies or standard second line hormonal therapy.

**STANDARD APPROACHES**

Patients treated with an antiandrogen as part of initial hormone therapy would benefit from antiandrogen withdrawal at PSA progression, which can lead to a decrease in PSA in approximately 20%. Second line hormone therapy has been widely used for several decades. This approach is attractive because of the easy administration and the low side effect profile. A common theme among all is suppression or blockade of adrenal androgens, including agents such as antiandrogens (bicalutamide, flutamide and nilutamide), steroids (prednisone and dexamethasone) and ketoconazole. To date no prospective, randomized studies have proved an overall survival advantage to these approaches. However, 20% to 60% of patients demonstrate significant PSA decreases of 50% or more and the drugs are not necessarily cross-resistant, allowing sequential use.

**INVESTIGATIONAL APPROACHES**

**Targeting the AR Axis**

Even patients with castration resistant disease have a functional AR axis due to increased intratumor ligand, mutated AR, over expressed AR or nonligand dependent activation. The biology underlying these pathways is beyond the scope of this review but it has been well summarized. Clinicians who have induced PSA decreases using the antiandrogens discussed or after antiandrogen withdrawal have capitalized on the functionality of the AR axis in this clinical state. As summarized, more effective strategies to target the AR axis represent an area of intense investigational activity (Appendix 1).

**Ligand inhibition.** Abiraterone acetate (Cougar Biotechnology, Los Angeles, California) is a specific inhibitor of the 17a-hydroxylase/c17-20-lyase enzyme complex responsible for adrenal androgen production. It is a more specific inhibitor of androgen synthesis than ketoconazole, may have fewer adverse effects and may not require steroid hormone supplementation. This oral, once daily drug has undergone phase I single and repetitive dose testing. In 4 of 6 castrate men a single dose of 500 mg was able to suppress testosterone to target levels. It appeared that the drug effectiveness may lie in its use to maximally suppress testosterone in men on gonadotropin-releasing hormone agonists and phase II studies are now opening at several centers.

**Targeting AR production and stability.** Another method of manipulating AR is not through the ligand, but through AR synthesis and stability. Hsp90 is responsible for maintaining active conformation of steroid receptors such as AR and estrogen receptor. Other client proteins include HER-2/neu, Raf protein kinase, cyclin D1, Akt, c-Met and epidermal growth factor receptor. The ansamycin antibiotics, such as 17-AAG (17-N-allylamo-17-demethoxygeldanamycin) (Kosan Biosciences, Hayward, California), inhibit Hsp90. Preclinical data demonstrated that 17-AAG degrades Hsp90 client proteins such as AR and phase I studies have been performed in which doses up to 157 mg/m² were shown to be tolerable and achieve serum concentrations in excess of those that suppressed AR in animal models. Phase I studies using the ansamycins are approaching completion alone and in combination with taxane chemotherapy.

**Inhibiting AR expression at the transcriptional level.** Gene transcription, including AR expression, can be regulated by modifying histones, the central core around which chromatin is wrapped. A new class of drugs known as HDAC inhibitors was developed to target a key enzyme in this process. In LNCaP prostate cancer cell lines HDAC inhibitors acetylated Hsp90, leading to AR depletion and reduced levels of Her-2, AKT and Raf-1 proteins, blocked androgen induced PSA production, inhibited cell proliferation and induced apoptosis. Suberoyanilidide hydroxamic acid (Merck, Whitehouse Station, New Jersey) is a small molecule inhibitor of HDAC that has shown activity in prostate cancer cell lines and in vivo xenograft models of human CWR22 prostate cancer cells. It can be given orally and was shown to be safe and well tolerated in doses sufficient to inhibit HDAC activity in phase I trials of patients with refractory solid tumors. It is currently being studied in a phase II multicenter trial of patients with advanced prostate cancer.

**Targeting Cell Signaling and Growth Dysregulation**

Progression through nonAR related growth mechanisms, such as dysregulation of growth factor receptor mediated
cell signaling, provides abundant opportunities to develop targeted therapies. An example of this is the phosphatidyl-inositol 3-kinase pathway, which has been implicated in the progression of prostate cancer. It is regulated by the tumor suppressor gene PTEN, which is frequently lost in advanced prostate cancer. Ultimately mutations in this pathway promote sustained activity in mammalian target of rapamycin, causing an increase in the transcription and translation of hypoxia inducible genes, and leading to cell growth and proliferation. Two rapamycin analogues, everolimus (Novartis International AG, Basel, Switzerland) and temsirolimus (Wyeth, Madison, New Jersey) are currently in phase II testing.

Immune Based Strategies
The exploitation of active immunity is an attractive strategy because vaccine therapy has low toxicity and patient appeal, and it may prolong the time to chemotherapy initiation. Sipuleucel-T (Provenge®) is a vaccine composed of autologous dendritic cells primed with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor fusion protein. In a phase III, randomized, placebo controlled clinical trial of 127 asymptomatic, progressive, metastatic, castration resistant patients with prostate cancer, although the primary end point of time to progression was not met (11.7 and 10.0 weeks for those receiving vaccine and placebo, respectively, p = 0.052), median survival was 25.9 months for those receiving vaccine vs 22 months for those in the placebo group at 36 months (p = 0.01). This demonstrates a statistically significant overall survival advantage for the treated cohort. However, because the study primary end point of time to progression was not met and the study was not originally powered to detect a survival difference, this finding must be validated in future studies.

Although this strategy focuses on stimulating specific T-cell sensitization, another approach focuses on releasing inhibitory controls on T-cell activation by manipulating CTLA4. CTLA4 is a negative co-regulator of the T-cell pathway that appears on the surface of T cells after activation. It may have a role in abrogating the immune response. MDX-010 (Medarex, Princeton, New Jersey) is a human IgG1 anti-CTLA4 monoclonal antibody. Clinical development is ongoing for evaluating multiple dose strategies alone and in combination with other modalities, such as chemotherapy and vaccines.

Bone Directed Therapy
Delaying the progression of metastatic disease, particularly in bone, may have significant impact on morbidity and mortality. Osteoblasts in metastatic prostate cancer have high levels of ET-1 receptor and signaling through the ET-1 pathway may contribute to increased osteoblastic activity and osseous metastasis progression. Atrasentan (Abbott Laboratories, Abbott Park, Illinois) is a selective ET-1 receptor antagonist. Phase II studies suggested that atrasentan could delay biochemical progression relative to placebo (155 to 71 days, p = 0.021). However, a formal, phase III study in 809 patients used a controversial composite end point that mandated discontinuation of therapy when patients had new bone scan findings regardless of other clinical outcomes, obfuscating data interpretation. Atrasentan is currently being studied in a Southwest Oncology Group phase III, double-blind, placebo controlled trial comparing docetaxel plus prednisone with and without atrasentan.

Another potential target for inhibiting metastatic spread to bone is RANK (receptor activator of nuclear factor-κB) ligand. Denosumab (Amgen, Thousand Oaks, California) is a fully human monoclonal antibody of the IgG2 subtype with high affinity for human RANK ligand. It was been shown to decrease bone turnover in postmenopausal women with low bone mineral density in phase II trials and it is now in phase III testing.

Taxane and Nontaxane Based Chemotherapy

Taxane based combination therapy. The current standard of care in the treatment of metastatic castration resistant prostate cancer is docetaxel, which has become the building block of combination therapy with multiple biological agents that are diverse in their mechanism of action. Current median survival benefits with standard docetaxel are modest, increasing survival by only 2 to 3 months, and the duration of effect is a short 6-month period. These limitations drive a search for more durable and efficacious taxane based combinations, as shown in Appendix 2. Select regimens are described.

Combinations with antiangiogenic targets. With the advent of bevacizumab, an antiVEGF humanized monoclonal antibody, inhibiting tumor growth through antiangiogenic approaches has proved to be an effective strategy for other tumor types. In prostate cancer VEGF is found in the metastatic tumors and plasma of patients with metastatic disease, and increased expression may correlate with disease progression. The combination of bevacizumab, docetaxel and estramustine demonstrated a PSA decrease rate of 65% and an objective response rate of 58%. Bevacizumab is currently being evaluated in a multicenter, phase III, randomized, placebo controlled, double-blind clinical trial in combination with docetaxel.

Combinations with vitamin D receptor element targets. Preclinical models demonstrated the antiproliferative activity of calcitriol and its ability to induce apoptosis and decrease angiogenesis and tumor invasion. A 250 patient, randomized, double-blind, placebo controlled, phase II trial of weekly high dose calcitriol (DN 101, Novacea, South San Francisco, California) plus weekly docetaxel vs docetaxel plus placebo showed no significant difference in the 2 treatment arms in patients achieving the primary end point, that is a PSA response of 50% or more at 6 months. However, median survival was estimated to be 24.5 months for those receiving DN 101 plus docetaxel vs 16.4 months for those treated with docetaxel alone (multivariate HR 0.67, p = 0.035). Currently DN-101 is in randomized, multicenter, phase III testing in combination with docetaxel vs docetaxel plus placebo.
Nontaxane Based Chemotherapy

Novel nontaxane based chemotherapeutics may offer a benefit for patients with taxane naïve, progressive, castration resistant prostate cancer. Epothilones are a new class of tubulin polymerizing agents. There are several epothilones undergoing evaluation. Showing promising activity is ixabepilone (Bristol-Myers Squibb, New York, New York) with significant objective responses and PSA decreases in 33% to 48% of patients as a single agent, and 69% in combination with estramustine in phase II clinical testing of chemotherapy naïve patients.\textsuperscript{41,42} The halichondrin B analogue, E7389 (Eisai Research Institute, Andover, Massachusetts) also targets the microtubule, inhibiting polymerization and leading to decreased tumor proliferation through the blockade of cell cycle progression at G2-M. Phase II studies of this agent are planned.\textsuperscript{43}

Bcl-2 inhibition is third pathway being explored to disrupt microtubule integrity and potentially abrogate docetaxel resistance. One such agent is oblimersen sodium (Genta, Berkeley Heights, New Jersey), which is an antisense oligonucleotide directed to Bcl-2 mRNA. A phase II trial showed a median survival of 19.8 months in 28 taxane naïve, metastatic, castration resistant patients receiving the combination of oblimersen and docetaxel.\textsuperscript{44} A European Organisation for Research and Treatment of Cancer phase II, randomized trial of docetaxel plus oblimersen vs docetaxel alone has completed accrual.\textsuperscript{43}

CONCLUSIONS

Patients in the clinical state of chemonaïve, castration resistant, metastatic prostate cancer represent a significant proportion of patients currently seen in the clinic. It remains unclear who should be treated early with docetaxel and who can be treated with deferred strategies taking advantage of noncytotoxic approaches. However, this setting clearly represents a therapy window of opportunity to evaluate novel treatments. Therapeutic decisions must consider patient symptoms and disease burden, and the risk of imminent disease related morbidities.

As our knowledge of the biology of this disease is expanding, so is the experimental therapeutic armamentarium that is available for patients with castration resistant, metastatic disease, such that chemotherapy is not the only choice, but rather 1 of many possible choices. Central to defeating prostate cancer is the commitment to continued clinical/translational research in this area and offering all appropriate patients access to clinical trials.

APPENDIX 1

<table>
<thead>
<tr>
<th>Select Agents Targeting AR Axis Activation</th>
<th>Standard Treatment Options</th>
<th>Investigational Options</th>
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<tr>
<td><strong>Therapeutic Strategy</strong></td>
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<tr>
<td>Androgen antagonists</td>
<td>Bicalutamide</td>
<td>BMS-641988</td>
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<td>Adrenal steroidogenesis</td>
<td>Flutamide</td>
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<td>inhibitors</td>
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<td><strong>Antigen 4</strong></td>
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<td><strong>Anti-insulin-like growth factor-1</strong></td>
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<td><strong>ET-1</strong></td>
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<td><strong>HDAC</strong></td>
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<td><strong>Angiogenesis/platelet-derived growth factor/VEGF</strong></td>
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APPENDIX 2

Select Open Clinical Trials of Taxane Combinations With Biological Therapies

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<tr>
<th>Therapeutic Strategy</th>
<th>Agent</th>
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<tbody>
<tr>
<td>Differentiation agent</td>
<td>DN101</td>
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<tr>
<td>Bcl-2 inhibition</td>
<td>AT-101</td>
</tr>
<tr>
<td>Epidermal growth factor receptor</td>
<td>Erlotinib</td>
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<tr>
<td>Selective cytoxygenase-2 inhibitors</td>
<td>Celecoxib</td>
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<tr>
<td>Clusterin inhibitor</td>
<td>OXG-011</td>
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<tr>
<td>Farnesyltransferase inhibitor</td>
<td>SCH 6636</td>
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<tr>
<td>Anti-insulin-like growth factor-1</td>
<td>CP-751,871</td>
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<tr>
<td>Endothelin-1 receptor inhibitor</td>
<td>Atrasentan</td>
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<tr>
<td>Mitochondrial oxidation induction</td>
<td>Ixemox</td>
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<tr>
<td>HDAC inhibitor</td>
<td>IT-AAG, 17-DMAG</td>
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<tr>
<td>Angiogenesis/platelet-derived growth factor/VEGF</td>
<td>Valatinib (PTK787)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Dimethylaminoethane acetic acid</td>
<td>Sunitinib</td>
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<td>Imatinib</td>
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Abbreviations and Acronyms

- AR = androgen receptor
- CALGB = Cancer and Leukemia Group B
- CTLA4 = cytotoxic T lymphocyte-associated antigen 4
- ET-1 = endothelin 1
- HDAC = histone deacetylase
- Hsp90 = heat shock protein 90
- PSA = prostate specific antigen
- RANK = receptor activator of nuclear factor-κB
- VEGF = vascular endothelial growth factor

REFERENCES


42. Galisky MD, Small EJ, Oh WK, Chen I, Smith DC, Colevas AD et al: Multi-institutional randomized phase II trial of the epothi-


Taxane Refractory Prostate Cancer

Paul Mathew and Robert DiPaola

From the M. D. Anderson Cancer Center, Houston, Texas, and University of Medicine and Dentistry of New Jersey (RDP), Newark, New Jersey

**Purpose:** Although docetaxel based therapy has become established as a front line therapy choice based on large, randomized studies, published studies of second line therapy for taxane refractory disease are limited.

**Material and Methods:** The literature on the biology of taxane resistance and studies applied to prostate cancer were reviewed using a PubMed® search and proceedings from recent symposia.

**Results:** Although taxane resistance invariably emerges in the treatment of prostate cancer, a consensus working definition or classification does not exist. Although there is a body of knowledge on the mechanisms of action of taxanes and resistance pathways, there are few clinical or translational studies in prostate cancer adequately assessing the modulation of these mechanisms. Results of additional clinical trials are needed to define and improve the standard of care in the second line setting for castration resistant prostate cancer after docetaxel failure.

**Conclusions:** The validation of the microtubule as a target in prostate cancer implies that a finer understanding of specific mechanisms of efficacy and resistance may yield novel strategies. Taxane analogues that have greater antitumor activity and/or are less susceptible to drug resistance mechanisms than their prototypes are in development, as are nontaxane microtubule targeting agents and other agents directed against the mitotic spindle. Combinations of such agents may yield added efficacy but potentially added neurotoxicity. In contrast, combinations with drugs that inhibit cellular mechanisms of taxane resistance and vascular endothelial or tumor-stromal prosurvival interactions may have lower neurotoxic profiles. Although alternate classes of cytotoxic agents, eg satraplatin, are being studied, there is a strong imperative for translational studies in this setting.

*Key Words: prostate, prostatic neoplasms, taxane, drug resistance, microtubules*

Although it had been observed for several decades that therapeutic agents directed against the mitotic spindle have activity in CRPC, there has been until recently a paucity of large, randomized studies of the benefit of this strategy. Recent phase III studies that confirmed the survival benefit of docetaxel over mitoxantrone-prednisone therapy for CRPC marked an important watershed in the development of prostate cancer therapy.1,2 These studies laid the foundation for neoadjuvant and adjuvant studies of docetaxel for high risk, localized disease and novel docetaxel based combinations for castration resistant disease and other disease states. Despite the increasing prevalence of taxane resistant prostate cancer there are limited studies in this setting.

**METHODS**

The literature on the biology of taxane resistance and studies applied to prostate cancer were reviewed using PubMed searches and proceedings from symposia, including American Society of Clinical Oncology annual meetings. Search terms included prostate cancer, taxane, drug resistance, mechanism of action, microtubule, paclitaxel, docetaxel and second line. Search results were used to annotate our commentary.

**PROPOSED DEFINITION OF TAXANE RESISTANCE WITH RELEVANT PITFALLS**

For the purpose of harmonizing strategies that attempt to define advances in the second line setting it may be valuable to offer a working definition of taxane refractory disease but adequate practical and biological pitfalls exist to render such a definition unsatisfying. An appropriate definition of taxane refractory disease is evidence of disease progression during therapy or within 30 days of the last taxane dose. However, if a definition of disease progression on taxane therapy is defined prospectively as eligibility criteria, not all patients referred for trial consideration by their treating physicians may robustly fulfill such criteria, particularly when based in part on biochemical progression. The practical difference between a definition of taxane resistance and the definition of castrate resistance is that it is 1 thing to require maintenance of castration and await suitable increments in PSA and quite another to require repeat exposure to taxane to achieve a better definition of taxane resistance.

The impact of variations in the dose level, schedule and type of taxane on the definition of resistance is also lacking because well designed crossover studies that address these questions are lacking. Responses to docetaxel regimens at 75 mg/m² every 3 weeks following progression on a 30 mg/m² dose level administered weekly may be anecdotally observed. As with breast cancer, partial noncross-resistance between docetaxel and paclitaxel in prostate cancer is also apparent.3 The frequency and quality of responses in these settings have not been definitively determined. Although it has been reasonably assumed that resistance to a taxane combined with a novel biological agent implies taxane resistance, unless the nature of the interaction between the taxane and the biological agent is fully understood, such an
assumption may be flawed. Briefly, although a satisfying definition of taxane resistance may be elusive, in all studies that address this disease state prospective annotation of the dose, schedule, type of preceding taxane regimen and features that define progression is necessary.

AN APPROACH TO CLASSIFYING TAXANE RESISTANCE

Approximately 40% to 50% of CRPCs do not show substantive and sustained PSA decreases in response to a taxane and the median duration of response is limited at 6 to 9 months. The biological foundation for primary vs secondary resistance to taxanes in CRPC requires elucidation. Although primary resistance, which may be defined as progressive disease without any evidence of response, to 1 taxane may predict resistance to another taxane or cytotoxic agent, secondary resistance, defined as progressive disease after an initial response, may be less predictive. Preclinical studies have suggested that hormonal status (castrate vs noncastrate) may contribute to the biological determinants of taxane resistance and vice versa, such that resistance in the noncastrate setting may not imply resistance in the castrate setting. Thus, an annotation of hormonal status in a classification may be pertinent, given ongoing experimentation with taxanes in noncastrate settings.

MECHANISM OF ACTION OF TAXANES

Microtubules have a diverse set of roles in cellular physiology, including providing structural integrity as part of the cytoskeleton, and a transport system for proteins, vesicles and organelles. They are critically important for the formation of the mitotic spindle, which dictates the proper segregation of chromosomes during mitosis, making them one of the best known targets in cancer therapy. Microtubules are formed by polymerization of monomers into linear structures. The combined assembly and disassembly processes yield a state of dynamic instability that allows the growing or shortening of individual microtubules. Vinca alkaloids bind free β-tubulin monomers, preventing their incorporation in growing microtubules. In contrast, taxanes bind to β-tubulin already incorporated into microtubules, preventing disassembly, stabilizing the mitotic spindle and triggering apoptotic pathways. These pathways include inactivation of bel-2 via phosphorylation, activation of JNK, Raf-1, and caspase dependent and caspase independent apoptotic mechanisms. Differences between the taxanes may exist. Docetaxel has been shown in laboratory models to have a much higher affinity for β-tubulin than paclitaxel and it results in phosphorylation of bel-2 at lower concentrations. Despite these potential differences variations in molecular and cellular effects with taxane exposure arise from several additional variables, including drug concentration, dose schedule and the integrity of different cell-cycle check points. For example, such variations may mean that centrosomal function may be preferentially targeted over microtubule dynamics or cell death may follow mitotic slippage rather than mitotic arrest. Alternatively taxanes may function to target vascular endothelial cells. Low dose paclitaxel has demonstrated preferential activity against endothelial vs nonendothelial cells independent of microtubule effects and it has antiangiogenic effects in vivo. Metronomic schedules, such as with novel orally bioavailable taxanes, may seek to exploit this strategy.

RESISTANCE PATHWAYS

Multifactorial multidrug resistance refers to several mechanisms of resistance that operate simultaneously and it is likely that this term best describes taxane resistance. Impaired drug delivery, and diverse cellular and microenvironment specific mechanisms may contribute to taxane resistance. A reduction in increased tumor interstitial fluid pressure via remodeling of leaky chaotic neoplastic vasculature by antivascular agents has been proposed as a mechanism to improve tumor blood flow, drug delivery and efficacy in experimental systems.14,15

Taxanes are vulnerable to the broad cellular mechanisms of drug resistance, such as those mediated by the ABC family of drug transporters. Of 48 human ABC transporters in 7 distinct subfamilies (ABCA–ABCG) defined by sequence homology and domain organization only approximately 13 individual proteins have been implicated in drug resistance. These proteins include MDR1 (ABCB1), which encodes the p-glycoprotein, and MRPI (ABCC1). To date there is no definitive answer to the questions of whether ABC transporters largely account for taxane resistance in prostate cancer and whether therapeutic inhibition can successfully modulate taxane resistance in vivo.

Additional potential mechanisms of chemotherapy resistance to taxane therapy may depend on direct interaction with tubulin. Although at least 8 tissue and cell specific β-tubulin isotypes have been described, a switch from class I to class III predominance has been observed to result in decreased impairment of microtubule dynamic instability by paclitaxel. Further studies are needed to establish whether variations in β-tubulin isotypes or tubulin mutations contribute toward taxane resistance in prostate cancer. Recent in vitro studies have suggested that the antiangiogenic and proapoptotic protein thrombospondin-1, induced by exposure to taxanes and repressed by the putative resistance protein txr-1, may mediate taxane induced apoptotic response via binding and activation of the cell surface receptor CD47.19 The roles of txr-1 and thrombospondin-1 in modulating taxane efficacy in vivo require elucidation. The influence of p53 on taxane mediated cytotoxicity still warrants further study. p53 is activated when damage occurs to the mitotic spindle. Initially spindle damage activates a p53 independent check point at metaphase-anaphase transition, which prevents cells from progressing through mitosis until the completion of spindle formation. Some preclinical studies have demonstrated that the status of p53, especially mutant p53, may predict taxane and epothilone sensitivity. Escape from mitotic arrest to a G1-like state (mitotic slippage), followed by p53 dependent apoptosis, may also occur after taxane exposure and therapeutic strategies to promote this cell death pathway are being studied. Survival pathways that manage a large variety of genotoxic stressors, including hormone deprivation and radiation, may also mediate drug resistance to taxanes, eg bel-2 and bel-XX up-regulation, and phosphatidylinositol 3-kinaseAkt/mTOR activation. Many prior clinical studies have attempted to modulate such molecular mechanisms of resistance with agents that modulate the expression of bel-2 or other apoptotic proteins. The dire survival outcomes associated with...
suboptimal PSA nadirs after hormone ablation\textsuperscript{27} seem to infer a high frequency of linked resistance to subsequent cytotoxic therapy, including taxanes. Thus, molecular themes that define early CRPC are candidate mediators of primary taxane resistance, eg PTEN inactivation.\textsuperscript{28} Limited in vitro evidence exists to support the premise that the activation of phosphatidylinositol 3'-kinase signaling as a result of PTEN inactivation results in a higher profile of resistance to taxane therapy, such as through the induction of ABC transporter proteins.\textsuperscript{29} However, other common genetic lesions in prostate cancer, such as the recently described TMPRSS2/ER\textsuperscript{30,31} family of fusion proteins,\textsuperscript{30,31} may also be implicated in drug resistance. For example, ETS-1 has been implicated in cisplatin resistance\textsuperscript{32} and it cooperates with mutant p53 to up-regulate MDR1.\textsuperscript{33}

Although pharmacological and pharmacokinetic differences among the taxanes\textsuperscript{34} may explain variations noted in toxicity and efficacy, their poor solubility has required surfactant vehicles, which themselves contribute to adverse effects, alter the pharmacokinetics of the parent drug and potentially affect efficacy.

**MANAGEMENT OF TAXANE REFRACTORY DISEASE**

**Practical Considerations**

Although there is no standard of care established in the taxane refractory disease state, practical considerations require a reappraisal of the threat of the disease, existing comorbidities, palliative imperatives and available therapeutics. A review of the dose, schedule and type of taxane regimen administered is important to assess whether a revised taxane based approach might be reasonable. In the few men in whom castration therapy has lapsed the reapprication of such therapy may be wise, although not necessarily effective. Inadequately explored secondary hormonal therapies, such as antiandrogens, ketoconazole with or without prednisone, or dexamethasone, may be considered but data supporting a survival benefit are lacking. For patients in whom small cell histological evolution has occurred, studies have demonstrated a clinical effect with etoposide-cisplatin therapy.\textsuperscript{35,36} Men with bone dominant symptomatic disease may obtain a palliative benefit from radioisotope and/or external beam radiation therapy but with the risk of limitation in marrow reserve and cytotoxic options. For men with good performance scores and preserved organ function enrollment in a clinical trial incorporating novel strategies in this setting is desirable, although most current larger CRPC studies formally exclude prior taxane exposure. An alternate taxane or antitubular agent or an alternate cytotoxic regimen with demonstrated activity in CRPC, eg cyclophosphamide based therapy,\textsuperscript{37,38} may be considered. However, evidence supporting survival or quality of life benefit is similarly lacking. Clearly treatment in the setting of taxane resistant disease should include careful discussion with patients regarding the current but limited data available in this setting along with a discussion of options for clinical trials.

**Results of Chemotherapy in the Second Line Setting After Taxane Therapy**

Although some physicians have considered mitoxantrone to be a de facto standard option for men with taxane resistant CRPC, few studies of mitoxantrone in this setting have been published. In 1 study men with CRPC with disease progression during or within 60 days of stopping taxane therapy were randomized to mitoxantrone-prednisone or ixabepilone (an epothilone B analogue) with a primary end point of a PSA decrease of 50% or greater by consensus criteria.\textsuperscript{39} Of 41 evaluable patients in each arm 17% in the ixabepilone arm and 20% in the mitoxantrone-prednisone arm showed these PSA decreases with an overall median survival of 13 and 12.5 months, respectively. Similar PSA based response (15%) and overall survival outcomes (13 months) have been reported in a retrospective series of second line chemotherapy in men who received an initial antimicrotubule regimen.\textsuperscript{40} Interestingly a retrospective report of outcomes with second line taxane therapy after prior ixabepilone therapy in 49 patients showed a 50% or greater PSA decrease in 51% with a median time to PSA progression of 4.6 months.\textsuperscript{41} Although this was retrospective and compared only historically, the result appears higher than the reverse sequence of taxane followed by epothilone reviewed earlier. However, 43% of the patients receiving second line taxane therapy discontinued therapy secondary to ixabepilone toxicity or personal preference alone and response rates in this group were 2-fold the rates in men who discontinued therapy for disease progression. In a similar vein in this study men with an initial response to ixabepilone had a higher probability of response to second line taxane therapy. Together these data suggest that, although there is considerable overlap in drug resistance among antimicrotubule regimens, including epothilones and taxanes, the clinical significance of this partial noncross-resistance has not been fully defined.

Combinations of taxanes and biologically active compounds are of considerable interest in CRPC. Thalidomide is an antiangiogenic and immunomodulatory molecule with diverse actions that may influence tumor-stromal interactions mediating drug resistance. A regimen of paclitaxel and estramustine combined with thalidomide was studied in a phase I–II setting in men with CRPC and prior chemotherapy.\textsuperscript{42} Of the 38 men 29 (76%) had a 50% PSA decrease, including 9 (64%) of 14 refractory to prior taxane therapy (7 of 8 refractory to docetaxel and 2 of 6 refractory to estramustine-paclitaxel) and 5 (28%) of 18 who had an objective partial response. These observations suggested that thalidomide has the potential to modulate taxane resistance. However, although these response rates appeared promising, overall median time to progression was only 3 months and median survival was 13.6 months. Translational studies of thalidomide and its highly potent immunomodulatory derivatives in taxane refractory models are of interest and further clinical trials in the second line setting are in progress. Imatinib is a platelet-derived growth factor receptor inhibitor that has been shown to overcome taxane resistance in orthotopic models of prostate cancer bone metastases by inhibiting tumor vascular endothelial platelet-derived growth factor receptor and inducing endothelial cell apoptosis.\textsuperscript{43} However, the equivalent clinical experiment of crossover from docetaxel alone to docetaxel and imatinib at disease progression did not demonstrate substantive PSA decreases or durable disease control.\textsuperscript{44} suggesting that the
gap between preclinical and clinical models of taxane resistance must be bridged.

The overlap in drug resistance mechanisms among antimicrotubule agents suggests that alternate classes of cytotoxics may have a higher therapeutic index. Early studies with the orally bioavailable platinum analog satraplatin suggested improved progression-free survival outcomes over those of prednisone, while a phase III trial has been completed in men with prior chemotheraphy and final results are awaited.45 There are no definitive reports on outcome with cyclophosphamide based therapy after docetaxel failure.

Briefly, the results of cytotoxic therapy in the second line setting have demonstrated that CRPC in general is poorly controlled after resistance to front line therapy with a time to progression of 3 months or less with second line therapy and a median survival of approximately 12 months. Improvements in these outcomes are clearly required.

**FUTURE DIRECTIONS**

The developmental landscape of therapy relevant to taxane refractory disease presents different considerations. Validation of the microtubule as a target in prostate cancer implies that a finer understanding of specific mechanisms of efficacy and resistance may yield novel strategies. Taxane analogues that may have greater antitumor activity and/or are less susceptible to drug resistance mechanisms than their prototypes are in development.46 Questions have been raised of whether these agents represent anything more than “old wine in a new bottle.”47 That is, in addition to decreased drug administration related challenges and altered toxicity profiles, whether those agents that are poor substrates for drug transporters will achieve major incremental efficacy must be tested. Nontaxane microtubule polymerizing agents, including the several epothilones, discodermolide, dolastatins, halichondrin B, and other agents directed against the mitotic spindle, e.g., mitotic kinesin and aurora kinase inhibitors, are also being studied.48–50 Combinations of such agents may yield added efficacy but potentially added toxicity as well, specifically neurotoxicity. In contrast, combinations with drugs that inhibit cellular mechanisms of taxane resistance, vascular endothelial or tumor-stromal prosurvival interactions may have lower neurotoxic profiles and such studies are currently in progress.

**EXPERIMENTAL CONSIDERATIONS**

A plethora of drugs, including tyrosine kinase inhibitors and antivascular agents, many with the theoretical potential to modulate taxane resistance, are currently being studied in the front line setting for CRPC.51 Most of these novel agents are understandably being studied in combination with the Food and Drug Administration approved regimen of docetaxel-prednisone. However, it is by no means apparent that each novel agent interacts favorably with this particular taxane-steroid regimen or that this represents the ideal pathway for investigating each agent. It follows that, if there is an approved agent in the second line setting, this will similarly spur the proliferation of studies of novel combinations with that agent.

Alternative perspectives for drug development are needed in taxane refractory disease, keeping in mind the potential benefits and yet significant limitations of preclinical models for predicting outcomes and explaining resistance. The neoadjuvant model of investigation in the high risk localized setting offers an opportunity for validation of candidate markers of resistance to taxane therapy and serves as a therapeutic platform for the study of novel agents that interdict putative mechanisms of resistance. In this regard the need for biomarkers that predict improved outcomes with neoadjuvant interventions has not decreased. Although it is plausible that it is in this disease setting advances based on tissue based interrogation can best be made, specific tumor-stromal interactions in metastatic microenvironments, such as bone, may also mediate distinctive drug resistance pathways and novel trial designs are required to anticipate this possibility. Lead-in strategies with novel compounds that target specific tumor-stromal interactions may allow the assessment of biomarker modulation specific to such an interaction before the introduction of combination cytotoxic therapy. This paradigm of investigation is currently under scrutiny. Importantly more rigorous bidirectional cross-talk between observations from clinical experimentation and laboratory modeling of these events is needed to infuse new directions in thinking and refine strategic goals. In this regard the boundaries and impediments between clinical and laboratory investigation must be softened and perhaps altogether dissolved.

**Abbreviations and Acronyms**

| ABC | adenosine triphosphate-binding cassette |
| CRPC | castration resistant prostate cancer |
| PSA | prostate specific antigen |

**REFERENCES**


Bone Directed Therapies for Prostate Cancer

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Purpose: Bone is the most common site of metastatic disease in prostate cancer and the lead cause of significant morbidity. Preclinical and clinical studies have provided insight into the pathophysiology of bone metastases and the changes that occur in the bone microenvironment that result in a favorable site of growth for prostate cancer. We provide an overview of recent advances in understanding bone biology, and bone targeted therapy research and development.

Materials and Methods: We reviewed recent research findings related to the biology of bone metastases, approaches to targeting osteoclast function, approaches to targeting osteoblasts and advances in assessing the treatment response to bone targeted therapies in the context of prostate cancer management.

Results: To date targeting some of the key players in the bone microenvironment has not been associated with a significant antitumor effect or with meaningful clinical benefit in phase III randomized trials. A significant limitation in the development of bone targeted therapy has been the inability to objectively assess treatment response. Investigation of improved imaging techniques are ongoing to provide better treatment assessment and, therefore, allow more rapid drug screening and development.

Conclusions: It is our recommendation that future therapy development should be combination based, focusing on simultaneous targeting of multiple relevant pathways. Most important of all is the direct targeting of prostate cancer cells.

Key Words: prostate, prostatic neoplasms, bone and bones, neoplasm metastasis

In 2007 an estimated 27,050 men will die of prostate cancer in the United States.1 Although patients with nonmetastatic prostate cancer have relatively higher survival rates, patients with metastatic disease do not fare as well. Several novel approaches to treatment are being investigated and they are discussed in other sections of this supplement. We reviewed the rationale and use of bone targeted therapy.

Bone is the most common site of metastatic disease in PCa, affecting 85% to 90% men with metastases,2,3 and it is a cause of significant morbidity. Preclinical and clinical studies have provided insight into the pathophysiology leading to the development of bone metastases and the changes that occur in the bone microenvironment that result in a favorable site of growth. By exploiting these changes innovative therapeutic approaches have been and continue to be investigated (see Appendix).

Biology of Bone Metastases

Preclinical and clinical studies have uncovered a complicated system of multiple interacting proteins and pathways that contribute to the development of bone metastases.4–11 The relative role of each is still being investigated, although a general understanding has been established. After prostate cancer cells arrive in bone 4 major players are involved in establishing metastases, including cancer cells, osteoblasts, osteoclasts and mineralized bone matrix, which is a major source of immobilized growth factors. Prostate cancer cells secrete factors that stimulate the osteoblast to proliferate, differentiate and secrete growth factors, which are deposited into the bone matrix and also enrich the local microenvironment of tumor cells (see figure). It is recognized that metastases result from a heterogeneous mixture of osteoblastic and osteolytic lesions.5,12–14 Histomorphometric evidence indicates that osteoblastic metastases form on trabecular bone at sites of previous osteoclast resorption and such resorption is required for subsequent osteoblastic bone formation.15,16 These findings suggest that PCa induces bone production through an overall increase in bone remodeling.6,17–19

When PCa cells metastasize to bone, they initially induce osteoclastogenesis and bone resorption. RANK, its ligand RANKL and its soluble decoy receptor OPG are essential regulators of this process.7 RANK-RANKL signaling is required for osteoclast differentiation from hematopoietic cells, activation of mature osteoclasts, osteoclast survival and cross-talk with other ligand receptor pathways affecting bone homeostasis.6,7 As bone is broken down through osteoclastic activity, a variety of growth factors present in bone are released into the microenvironment, providing fertile soil supporting the further proliferation of prostate cancer cells and promoting osteoblastic activity.5,20 Differentiation of osteoblasts is regulated by many factors. Some of the better described factors are bone morphogenic proteins, ETs, transforming growth factor-β, fibroblast growth factors,
platelet derived growth factors, insulin-like growth factors and their receptors. Additionally, other proteins work indirectly to enhance bone production, including PSA, urinary plasminogen activator, serine proteases and parathyroid hormone related proteins. Eventually osteoblast mediated bone mineralization outweighs osteoclast mediated bone resorption, resulting in a predominance of osteoblastic lesions. However, unlike normal lamellar bone, which is composed of collagen bundles that are organized in tightly packed linear fashion, increased osteoblast activity in PCa results in the production of woven bone, which is composed of loosely packed, randomly oriented collagen bundles with suboptimal strength. The combination of increased osteolysis and the production of woven bone leads to the bone complications commonly seen in PCa. Targeting PCa induced dysregulation of bone turnover by focusing on the osteoclast and osteoblast has led to several therapeutic approaches.

**Targeting Osteoclast Function**

Several commercially available and investigational drugs that inhibit the function of osteoclasts directly or indirectly, resulting in decreased bone resorption, are in different stages of investigation for the treatment and prevention of skeletal complications. Predominantly being explored in the osteoporosis arena, many of these drugs are also of interest for treating bone metastases, given the importance of osteoclasts in metastasis development.

**Bisphosphonates**

Bisphosphonates are analogues of pyrophosphate, a normal constituent of bone matrix, which binds to hydroxyapatite crystals of bone, making them less available for osteoclast resorption. Bisphosphonates also decrease the life span of osteoclasts by promoting their apoptosis, ultimately resulting in decreased bone resorption. Zometa 039 was the first trial to demonstrate a role for bisphosphonates in the treatment of metastatic PCa. In this phase III trial 643 men with asymptomatic or minimally symptomatic HRPCa and evidence of bone metastases were randomized to zoledronic acid or placebo. At 15 months patients treated with zoledronic acid experienced fewer SREs, as defined by pathological fracture, spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic treatment for bone pain (33% vs 44%, p = 0.02). Results of this study led to Food and Drug Administration approval of zoledronic acid in patients with HRPCa and evidence of bone metastases. Investigations of other bisphosphonates at different PCa stages has been disappointing as single agents and in combination with hormones and chemotherapy, and they currently have no role in standard treatment for PCa (see table).

The role of zoledronic acid in earlier stage disease has not been clearly defined. Zoledronic acid has been shown to increase bone mineral density and suppress bone turnover markers during the first year of treatment in men receiving gonadotropin releasing hormone agonists when given every 3 months and as a 1 time dose. However, trials of clodronate and zoledronic acid for preventing bone metastases have been negative. The completion of additional stud-

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<tr>
<td>Zometa 039</td>
<td>Zoledronic acid vs placebo (all pts continued hormone therapy, additional antineoplastics permitted)</td>
<td>643</td>
<td>Androgen independent prostate cancer with asymptomatic or minimally symptomatic bone metastases</td>
<td>Proportion of men experiencing 1 or more SREs by 15 mos</td>
<td>Significant decrease in No. + time to SREs</td>
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<td>INT-05/CSP</td>
<td>Pamidronate vs placebo (additional hormone therapy + chemotherapy were permitted)</td>
<td>350</td>
<td>Androgen independent prostate cancer with symptomatic bone metastases</td>
<td>Decreased bone pain + narcotic use</td>
<td>No significant difference in pain, analgesic use or SREs Study was terminated early due to lower than expected event rate</td>
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<td>Zometa 704</td>
<td>Zoledronic acid vs placebo (gonadotropin hormone-releasing hormone agonists were continued, additional therapy at investigator discretion)</td>
<td>398</td>
<td>Progressive castrate, nonmetastatic</td>
<td>Time to first bone metastasis</td>
<td>Study was terminated early due to lower than expected event rate</td>
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<td>MRC Pr05</td>
<td>Clodronate vs placebo (standard hormone therapy was continued)</td>
<td>311</td>
<td>Androgen dependent, asymptomatic bone metastases</td>
<td>Symptomatic bone progression-free survival</td>
<td>Nonsignificant trend toward improved bone progression-free survival</td>
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<td>MRC Pr04</td>
<td>Clodronate vs placebo (standard hormone therapy was continued)</td>
<td>508</td>
<td>Standard treatment for stage T2–T4 disease with no evidence of bone metastases</td>
<td>Time to symptomatic bone metastases or PCa death</td>
<td>No significant difference in time to symptomatic bone metastases or overall survival</td>
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ies, such as Cancer and Leukemia Group B 90202, which is assessing zolendronic acid in patients with recently diagnosed stage D2 disease beginning androgen ablation therapy, will be required to better understand the effect of zolendronic acid in earlier stages of disease. Investigation of zolendronic acid in combination with other therapies are ongoing with promising preclinical results reported.33 Currently the role of bisphosphonates is palliative with no significant antitumor effect demonstrated. With more recently reported serious side effects of bisphosphonate therapy, including renal dysfunction and osteonecrosis of the jaw,31 it is important that zolendronic acid should only be used in clinically proven settings.32

Radiopharmaceuticals
Radiation therapy reduces tumor size, decreases osteolysis and decreases the skeletal tumor burden.33 Radiopharmaceuticals were developed as bone targeted therapy to provide systemic treatment of osseous lesions. Preferentially taken up at areas of exposed hydroxyapatite resulting from the metastatic process, radiopharmaceuticals deliver radiation to the entire tumor microenvironment, damaging not only cancer cells, but also the supporting cells of the microenvironment. Three radiopharmaceuticals are currently available in the United States, including 32P-phosphorus, 89strontium, 89Sr, strontium and 153samarium. These agents decay with varying half-lives, emitting either β or γ energy to destroy cancerous cells through apoptosis.10 Phase III trials of 89strontium34 and 153samarium35 have been completed. In the 2 trials radioisotope treatment was associated with decreased opioid usage and increased quality of life. However, no survival benefit or appreciable antitumor activity was appreciated. Of importance is that significant hematological toxicity was observed in these trials. Radiopharmaceuticals have also been combined with chemotherapy. In a phase II study of bone targeted consolidation therapy consisting of weekly doxorubicin with or without 89strontium after initial chemotherapy,36 patients receiving 89strontium had longer survival (27.7 vs 16.8 months, p = 0.0014). Based on the suggestion of improved survival a phase III trial is ongoing. To date the role of radiopharmaceuticals is palliative. An additional limitation to currently available radiopharmaceuticals is that significant, prolonged bone marrow suppression often follows treatment, precluding further systemic treatment with myelosuppressive agents in some patients.34,35,37

Targeting RANK-RANKL Signaling
Given the central role of RANK-RANKL signaling in osteoclast function, investigation of novel drugs targeting RANK-RANKL signaling are under development. Denosumab, a RANKL antibody, is being investigated in a variety of settings. In postmenopausal women with low bone mineral density treatment with denosumab resulted in increased bone mineral density and decreased bone resorption with no increased adverse effects compared to placebo.38 Other ongoing trials include a phase III noninferiority study comparing denosumab with zoledronic acid in patients with HRPCa and bone metastases (NCT00321620) and a phase II study testing the effect of denosumab on prolonging bone metastasis-free survival in men with nonmetastatic HRPCa (NCT00286091).

Studies of other inhibitors of RANK-RANKL signaling including synthetic OPG (Fc-OPG fusion molecule) and RANK-Fc, are ongoing for the treatment of osteoporosis although, given the importance of bone resorption in bone metastasis, they are likely to also be investigated in this setting.39

MMPs
In PCa MMPs have been shown to be involved in invasion and metastasis, and contribute to bone remodeling dysregulation.9,40 A specific MMP, MMP-7, identified at the tumor-bone interface, has been shown to process RANKL to a soluble form that promotes osteoclast activity through facilitating RANK-RANKL signaling.9 Preclinically MMP inhibition disrupts this process.40 These findings have led to the investigation of MMPIs in prostate cancer. BMS-275291 is a novel MMPI designed to inhibit a broad spectrum of MMPs.41 A phase II trial of BMS-275291 was recently reported in men with HRPCa and evidence of bone metastases.41 There were no responders according to PSA or measurable disease. Stable disease was noted at 8 weeks in 56% of patients. Biochemical markers of bone turnover were assessed, although due to the high rate of disease progression limited serial samples were available. Baseline bone markers had prognostic value. Although BMS-275291 as single agent therapy did not result in antitumor activity, the role of newer generation MMPIs as combination therapy may warrant further investigation.

Src Tyrosine Kinase Inhibitors
Src tyrosine kinase is a key enzyme in osteoclast dependent bone resorption.42 Therefore, Src tyrosine kinase inhibitors are being investigated for the treatment of osteoporosis, and for prevention and treatment of bone metastases.43 Preclinically Src tyrosine kinase inhibition leads to the inhibition of osteoclast mediated bone resorption and the stimulation of osteoblast mediated bone formation.43 Early studies of Src tyrosine kinase inhibition resulted in the inhibition of osteoclastic activity, demonstrating proof of principle.44 However, to date Src tyrosine kinase inhibitors have not been extensively investigated clinically.

Targeting Integrins
In prostate cancer integrins αvβ3 and αvβ5 are known to be essential molecules involved in metastases, regulating cell adhesion, migration, invasion and motility.45–47 αvβ3 has also been shown to be critical in osteoclast formation and activity.47 Blockage of human bone derived αvβ3 has been shown to significantly decrease the recruitment of osteoclasts in response to tumor cells as well as the degradation of calcified bone tissue.48 Cilengitide (EMD121974) is a potent and selective integrin antagonist. We are currently performing a randomized, phase II, National Cancer Institute sponsored, multi-institutional study (NCT00103337) to evaluate the role of cilengitide for treatment in men with asymptomatic metastatic HRPCa.49 Another study is evaluating it for nonmetastatic HRPCa (NCT00121238). Systemic markers of bone remodeling are being used to provide correlative evidence of the effect of cilengitide on bone.

Targeting Osteoblasts
Targeting the ET Axis
ET-1, a key component of the endothelin axis, has been identified as having an important role in the pathophysiol-
ogy of PCa, particularly in the development and progression of osteoblastic bone metastases. Increased ET-1 contributes to tumor growth and proliferation, inhibits apoptosis, enhances angiogenesis and other growth factors, is thought to be crucial in the development of bone metastases and has been reported to be a cause of bone pain. ET-1 acts by binding to ET receptor and activating downstream signaling. Atrasentan is a potent, selective, orally bioavailable inhibitor of ET receptor that is being investigated for HRPCa.

In a randomized phase II trial 288 asymptomatic men with metastatic HRPCa were randomized to atrasentan (2.5 or 10 mg per day) or placebo. The primary end point was time to clinical progression, determined by a disease related intervention or the appearance of new radiographic lesions. Based on ITT analysis a nonsignificant trend toward increased TTP was demonstrated for patients treated with 10 mg per day (183 vs 137 days, p = 0.13). When only the 244 evaluable patients were included, a significant increase in TTP was shown for patients in the 10 mg per day group (196 vs 129 days, p = 0.021). For the ITT and evaluable populations there was an increase in time to PSA progression in patients treated with 10 mg atrasentan per day (71 vs 155 days, p = 0.002). In a larger phase III trial 809 patients with HRPCa were randomized to 10 mg atrasentan per day vs placebo. Based on ITT analysis a nonsignificant trend toward increase in TTP was demonstrated (HR 1.14). When analysis was limited to patients with bone metastases, a significant increase in TTP was demonstrated for patients treated with 10 mg per day (183 vs 137 days, p = 0.13). When only the 244 evaluable patients were included, a significant increase in TTP was shown for patients in the 10 mg per day group (196 vs 129 days, p = 0.021). For the ITT and evaluable populations there was an increase in time to PSA progression in patients treated with 10 mg atrasentan per day (71 vs 155 days, p = 0.002). In a larger phase III trial 809 patients with HRPCa were randomized to 10 mg atrasentan per day vs placebo. Results from a phase III trial investigating the role of atrasentan to delay disease progression in men with nonmetastatic HRPCa are awaited (M00-244).

Given the demonstrated biological activity on osteoblasts, as reflected by suggested effects in patients with PCa who have bone metastasis but lack of a demonstrable antitumor effect, the usefulness of this agent must be defined in the context of combination therapy. Preclinical studies have shown additive effects of atrasentan in combination with docetaxel. A phase III trial (Southwest Oncology Group 0421) is testing the hypothesis that combined targeting of PCa cells, osteoblasts and osteoclasts using docetaxel plus atrasentan plus zoledronic acid is superior to docetaxel plus placebo with regard to survival and progression-free survival.

Assessing Treatment Response to Bone Targeted Therapies

As the potential treatment armamentarium available has increased to include targeted therapeutics that may not be cytotoxic, standard clinical end points of efficacy such as tumor response rates may not be as applicable for assessing the treatment response. Therefore, other measures of efficacy to aid in assessing treatment responses are needed, especially in bone targeted therapy. Two possible strategies to improve treatment assessment are the investigation of biochemical markers of bone turnover and improved imaging modalities.

Biochemical Markers of Bone Turnover

Investigation of markers of bone resorption and formation reflecting osteoclastic and osteoblastic activity, respectively, may be a useful tool for measuring the efficacy of bone targeted therapy in PCa, given the overall increase in bone turnover resulting from metastases, as described. The premise is that baseline levels of bone metabolism markers may be of prognostic value, while serial levels of these markers may predict enhanced response and/or survival in response to bone targeted therapy. Increased markers of osteolytic activity (N-telopeptide) and osteoblastic activity (bone specific alkaline phosphatase) have been associated with adverse clinical outcomes, including shorter time to skeletal events, disease progression and death. Additionally, a correlation between baseline values of N-telopeptide, bone specific alkaline phosphatase, PSA and the number of bone lesions has also been shown, suggesting that baseline levels correlate with tumor burden. Investigation of bone markers in recent studies of bone targeted therapy has demonstrated the suppression of biochemical markers of bone turnover, supporting the potential role of bone turnover markers for investigating the efficacy of novel agents.

Imaging

Although it is considered to be the standard imaging modality to assess for skeletal metastases, it is well recognized that bone scanning lacks the specificity needed to accurately distinguish metastatic lesions and evaluate the treatment response. An investigative approach is the use of diffusion MRI technology to assess response. Diffusion MRI monitoring of antitumor therapy is based on detecting changes in the Brownian motion of water in the tumor. During the course of successful therapeutic intervention changes in cellular structure occur that precede macroscopic changes such as decreases in overall tumor volume. These changes are detectable as a quantifiable change in the apparent diffusion coefficient of tumor water. To overcome the heterogeneity of the tumor response fDM was developed as a statistical approach for segmenting tumors based on a defined threshold of the apparent diffusion coefficient of tumor water change following therapy. Results in patients with primary malignant brain tumors have been analyzed using the fDM approach, revealing that fDM could be used to stratify patients as responsive or nonresponsive to therapy in as early as 3 weeks into a 6 to 7-week fractionated therapy schedule. Using PC3 prostate cancer xenografts with confirmed bone metastases our group has observed a correlation between changes in fDM and changes in bioluminescence imaging in response to docetaxel treatment with changes seen by day 7 (unpublished data). Thus, a clinical trial investigating this methodology in men with metastatic prostate cancer is planned at University of Michigan.

Other imaging protocols under investigation include 11 carbon acetate and FDG PET of bone in patients with bone dominant metastatic PCa (NCT00392938), comparison of FDG PET/computerized tomography to conventional imaging to assess the treatment response in metastatic PCa (NCT00282906), comparison of 11 carbon-methionine and FDG PET to standard imaging in men with metastatic PCa (NCT00029891) and comparison of PET/computerized tomography and whole body MRI for detecting skeletal and soft tissue metastases (NCT00375830).
CONCLUSIONS

In prostate cancer bone directed therapy is a rational experimental approach. However, it is important to highlight that to date targeting some of the key players in the bone microenvironment have not been associated with a significant antitumor effect or with meaningful clinical benefit in phase III randomized trials. It is our recommendation that future therapy development should be combination based, focusing on the simultaneous targeting of multiple relevant pathways. Most important of all is the direct targeting of prostate cancer cells.

APPENDIX

Potential Targets for Bone Directed Therapy

<table>
<thead>
<tr>
<th>Target</th>
<th>Potential Therapy</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoclast function</td>
<td>Bisphosphonates4,24,25,26,29,66,67</td>
<td>Phase III</td>
</tr>
<tr>
<td>Inhibit osteoclast function</td>
<td>Denosumab30</td>
<td>Phase III</td>
</tr>
<tr>
<td>RANK/RANKL signaling</td>
<td>Synthetic OPG66</td>
<td>Being studied in osteoporosis, preclinical</td>
</tr>
<tr>
<td>MMPs</td>
<td>BMS-27529141</td>
<td>Phase II</td>
</tr>
<tr>
<td>Src tyrosine kinase</td>
<td>Src tyrosine kinase inhibitors43,44</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Integrins</td>
<td>Cilengitide (EMD121974)49</td>
<td>Phase II</td>
</tr>
<tr>
<td>Osteoblast function</td>
<td>Atrasentan57</td>
<td>Phase III</td>
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<tr>
<td>ET axis</td>
<td>AntiBMP antibodies71</td>
<td>Preclinical</td>
</tr>
<tr>
<td>BMPs</td>
<td>Increased noggin expression70</td>
<td>Preclinical</td>
</tr>
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<td>Wnt signaling pathway69</td>
<td>Novel inhibitors of Wnt</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Exposed hydroxypatite</td>
<td>Radiopharmaceuticals34,35</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ADC</td>
<td>apparent diffusion coefficient of tumor water</td>
</tr>
<tr>
<td>ET</td>
<td>endothelin</td>
</tr>
<tr>
<td>FDG</td>
<td>fludeoxyglucose 18F</td>
</tr>
<tr>
<td>fDM</td>
<td>functional diffusion mapping</td>
</tr>
<tr>
<td>HR</td>
<td>hormone refractory</td>
</tr>
<tr>
<td>ITT</td>
<td>intent to treat</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
</tr>
<tr>
<td>MPI</td>
<td>MMP inhibitor</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>OPG</td>
<td>osteoprotegerin</td>
</tr>
<tr>
<td>PCa</td>
<td>prostate cancer</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
</tr>
<tr>
<td>RANK</td>
<td>receptor activator of nuclear factor-κB</td>
</tr>
<tr>
<td>RANKL</td>
<td>RANK ligand</td>
</tr>
<tr>
<td>SRE</td>
<td>skeletal related event</td>
</tr>
<tr>
<td>TTP</td>
<td>time to progression</td>
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</tbody>
</table>

REFERENCES


