Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

OCTOBER 2014

DOCS DRIVE TREATMENT CHOICE IN PROSTATE CANCER

Physicians who diagnosed low-risk prostate cancer had more influence over the decision to enter active surveillance than did the disease characteristics, a review of 12,000 cases showed. Overall, about 20% of the men chose active surveillance as the initial approach to management. Rates of active surveillance among the diagnosing urologists varied from 4.5% to 64% of patients, according to Karen E. Hoffman, MD, MPH, of MD Anderson Cancer Center in Houston, and colleagues.

Analysis of factors that influenced treatment decision showed that the diagnosing physician had more than twice the impact on the choice of upfront therapy as compared with disease characteristics, as reported online in *JAMA Internal Medicine*.

"Primary care physicians who refer patients to urologists for prostate biopsy may assume that patients will receive similar management recommendations, regardless of the urologist they see," the authors said. "We sought to determine whether this is indeed the case."

They queried the Surveillance, Epidemiology and End Results database for men, ages 66 and older, with newly diagnosed low-risk prostate cancer during 2006 through 2009. Using Medicare-linked claims data, the authors obtained information on the diagnosing urologist, consulting radiation oncologist, cancer-directed therapy, and comorbidities.

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ADT HEADS LIST OF THERAPIES IN NEW PROSTATE CANCER GUIDELINE

Indefinite continuation of androgen deprivation therapy (ADT) remains the cornerstone of systemic treatment for metastatic castration-resistant prostate cancer (mCRPC), augmented by new agents, according to a joint guideline from US and Canadian oncology groups.

In addition to ADT (medical or surgical), clinicians should offer men with mCRPC abiraterone (Zytiga®) plus prednisone, enzalutamide (Xtandi®), and radium-223 (Xofigo®), all of which have favorable benefit-harm profiles, the guideline indicated. Men also may be offered docetaxel plus prednisone, but should be thoroughly informed of potential toxicity.

Other systemic agents have niche roles in the treatment of mCRPC, as recommended by the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO). The guideline was published online in the Journal of Clinical Oncology and is available on the ASCO website [www.asco.org].

"We have seen unprecedented progress against advanced prostate cancer recently, with six new treatments approved in the last couple of years," guideline panel co-chair Ethan Basch, MD, of the University of North Carolina at Chapel Hill, stated. "There are a lot of nuances about treatment selection in terms of disease stage and what prior therapies the patient received. We hope this guideline will help doctors and patients make informed treatment decisions."

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EXELIXIS ANNOUNCES RESULTS FROM THE COMET-1 PHASE 3 PIVOTAL TRIAL OF CABOZANTINIB IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Exelixis, Inc. announced top-line results from the final analysis of COMET-1, the phase 3 pivotal trial of cabozantinib in men with metastatic castration-resistant prostate cancer (mCRPC) whose disease progressed after treatment with docetaxel as well as abiraterone and/or enzalutamide. The trial did not meet its primary endpoint of demonstrating a statistically significant increase in overall survival (OS) for patients treated with cabozantinib as compared to prednisone. The median OS for the cabozantinib arm of the trial was 11.0 months versus 9.8 months for the prednisone arm (hazard ratio 0.90; 95% confidence interval [CI] 0.76–1.06; p = 0.212).

Cabozantinib inhibits the activity of tyrosine kinases including MET, VEGFRs and RET. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

The COMET-1 results are the subject of ongoing analyses. Exelixis will submit additional data, including secondary and exploratory endpoints, for presentation at a future medical conference. Besides OS, the exploratory endpoint of progression-free survival (PFS) as assessed by

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STUDY OF INTER- AND INTRA-OBSERVER REPRODUCIBILITY IN THE INTERPRETATION OF (^{18}F) CHOLINE PET/CT EXAMINATIONS IN PATIENTS SUFFERING FROM BIOCHEMICALLY RECURRENT PROSTATE CANCER FOLLOWING CURATIVE TREATMENT

Pegard C, Gallazzini-Crépin C, Giai J, et al

EJNMMI Res 4: 25, 2014

Background: The aim of this study was to investigate the reproducibility of intra- and inter-observer interpretation of (^{18}F) choline positron emission tomography/computed tomography examinations in patients suffering from biochemically recurrent prostate cancer following curative treatment.

Methods: A total of 60 patients with biochemical recurrence after curative treatment were included in this bicentric study. The interpretations were based on a systematic analysis of several anatomic regions and all four nuclear medicine physicians used identical result consoles. The examinations were interpreted with no knowledge of the patients' clinical context. Two months later, a second interpretation of all these examinations was performed using the same method, in random order.

Results: To evaluate local recurrences, when the prostate is in place, the results showed moderate inter- and intra-observer reproducibility: concordance of all four physicians has a Fleiss' kappa coefficient of 0.553 with a confidence interval of (0.425 to 0.693). For patients who had had a prostatectomy, there was excellent concordance for the negative examinations. For the lymphatic basin, inter- and intra-observer reproducibility was excellent with a Fleiss' kappa coefficient of 0.892 with a confidence interval of (0.788 to 0.975). The lymphatic sub-group analysis was also good. For the lymphatic groups in the right or left hemi-pelvices, all Fleiss' kappa and Cohen's kappa coefficients are varying from 0.760 to 1 with narrow confidence intervals from (0.536 to 0.984) to (1 to 1) in favour of good/excellent inter-observer reproducibility. To evaluate bone metastasis, inter-observer reproducibility was good with a Fleiss' kappa coefficient of 0.703 and a confidence interval of (0.407 to 0.881).

Conclusion: Our study is, at this time, the only one on the reproducibility of

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THE NUMBER OF CORES AT FIRST BIOPSY MAY SUGGEST THE NEED FOR A CONFIRMATORY BIOPSY IN PATIENTS ELIGIBLE FOR ACTIVE SURVEILLANCE-IMPLICATION FOR CLINICAL DECISION MAKING IN THE REAL-LIFE SETTING

Villa L, Salonia A, Capitanio U, et al

Urology 84: 634–641, 2014

Objective: To assess whether the number of cores at first prostate biopsy affect pathologic findings at radical prostatectomy (RP) in potential candidates for active surveillance (AS).

Material and Methods: Two hundred seventy-five patients fulfilling Prostate Cancer Research International: Active Surveillance criteria (prostate-specific antigen level ≤ 10 ng/mL, prostate-specific antigen density <0.2 ng/mL/cm^3, number of positive cores ≤2, T1c-T2 clinical stage, Gleason score [GS] ≤6) underwent RP between 2005 and 2013 at a single institution. Patients were stratified into three groups according to different biopsy schemes (≤12 vs 13-18 vs ≥19 cores). Rates of pathologically confirmed insignificant prostate cancer (pIPCa; defined as RP GS ≤6, tumor volume ≤0.5 mL, and organ-confined disease) and unfavorable disease (UD, defined as non-organ-confined disease and/or pathologic GS ≥7) at RP were stratified according to the biopsy schemes. Logistic regression analyses tested the effect of preoperative variables in predicting pIPCa and UD at RP.

Results: Of all, 23.3% and 33.4% patients harbored pIPCa and UD, respectively. pIPCa and UD were found in 15.7%, 32.1%, 25.3% (P = 0.04) and in 48.1%, 23.8%, 24.1% (P <0.001) patients with ≤ 12, 13-18, ≥19 cores, respectively. At multivariate analyses, number of biopsy cores emerged as an independent predictor of both pIPCa (≤12 vs 13-18 cores: odds ratio [OR] = 2.34; P = 0.02) and UD (≤12 vs 13-18 cores: OR = 0.39; P <0.01; ≤ 12 vs ≥19 cores: OR = 0.38; P <0.01).

Conclusion: Among candidates for AS, number of biopsy cores emerged as an independent predictor of pIPCa and UD at RP. These findings would suggest that the extent of initial biopsy sampling should be considered when addressing patients to AS and before planning any surveillance strategies.

NEW GUIDELINES IN MCRPC

(Continued from page 1)

Quality of life figured prominently in recommendations about therapies to use in addition to ADT, according to guideline co-chair Andrew Loblaw, MD, of Sunnybrook Odette Cancer Center in Toronto, Ontario, Canada. Patients need to understand the likely and potential side effects. Cost also will enter into discussions between clinicians and patients, because cost can affect access to treatment and quality of life.

The guidelines emphasize the situations under which specific therapies should be used (in addition to ADT):

- Abiraterone/prednisone, enzalutamide, and radium-223 should be offered to men who have disease that has spread predominately to bone; all three drugs have demonstrated improved survival, quality of life, and a favorable balance between benefits and harms.
- If chemotherapy is considered, docetaxel/prednisone should be offered and accompanied by a discussion of toxicity.
- If disease progresses on docetaxel, clinicians may offer cabazitaxel (Jevtana®), the side effects of which should also be discussed thoroughly.
- Sipuleucel-T (Provenge®) should be reserved for men with no or minimal symptoms.
- Mitoxantrone may be offered with patient understanding of the therapy's limited clinical benefit and risk of side effects.
- Clinicians may offer ketoconazole or antiandrogens but should clearly inform patients about expectations of limited clinical benefit and a risk of side effects.

Clinicians should not give patients with mCRPC bevacizumab (Avastin®), estramustine (Emcyt®), or sunitinib (Sutent®), according to the guideline. Palliative care should be discussed with all patients early in the course of the disease, along with other treatment options. The guideline panel found evidence insufficient to recommend a specific sequence for available therapies.

The ASCO-CCO guideline follows one developed by the American Urological Association in 2013, which also emphasized appropriate use of the expanded number of treatment options for men with mCRPC but addressed sequencing, as well.

MedPage Today, 8 September 2014

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"What is the best diet to lose weight and fight cancer? Atkins, Jenny Craig, South Beach, Mediterranean, Moyad Eat Anything in Moderation Plan, Vegan, Weight Watchers? YES !"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editor's note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line:

One diet does NOT fit all! Pick one that you can adhere to and if it makes you heart-healthy then you are the winner!

In one of the largest reviews of different diets to lose weight I have ever come across in my career, the results might surprise you or maybe not. It has become clear to me over 30 years that partially reducing your overall caloric intake, regardless of the source, is the key to weight loss and fighting cancer! In the old days (aka just a few years ago) the way to get someone to lose weight was simply by being honest and telling a person to remove certain foods from their diet to reduce calories.

Well, being honest does not work anymore. So, diets that rely on a system of "points" (aka calories) make people feel better; you're only allowed a certain number of "points" (aka calories) and if you exceed that number you will gain weight. As the days went on other distracting and non-honest terms came to light such as "glycemic index" in response to being told to only eat foods that cause minimal changes in insulin (aka lower calorie foods). However, the problem with all these fad diets is that they forget to mention the obvious—that simply reducing caloric intake from any source can help you lose calories. So, along comes the largest and most comprehensive review of diets in one of the most prestigious journals in the world; and it finds that whatever diet a patient can adhere to (as long as it helps lower calories) is the right one![1]

So, what does this means for the Moyad Diet and fighting cancer? The Moyad Diet is any diet you can adhere to that helps you do at least seven things: 1) Lose weight/waist, and/or 2) increase muscle mass, and/or 3) reduce or improve cholesterol, and/or 4) reduce or improve blood pressure, and/or 5) reduce or improve blood sugar (glucose), and/or 6) reduce blood markers/tests of inflammation such as hs-CRP and/or 7) keep your stress level low, and your mood stable and positive (not grouchy like some wacky guy that yells at a TSA agent because they stopped him to check out what he says is "only moisturizer so what is the big deal!").

All of these seven changes are exactly what can also help you fight cancer and potentially lower your PSA. I have NEVER believed that one diet fits all just like I have NEVER believed that one exercise fits all! I find it sad and troubling when some "experts" tell cancer patients that there is only one path to dieting and cancer and if you do not follow that specific path then you are in trouble. Well my friends, there are many paths to achieve success in dieting. Life is a terminal disease, my friends, and it is so, so short; and in fact too short to be told I cannot enjoy a little ice cream, pizza, beer and wings every once in a while—especially by some "expert(s)" that have the quality of life tantamount to a package of flavorless rice cakes (blaahhh)!

Reference:

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A TREATMENT OPTION FOR ADVANCED PROSTATE CANCER THAT HAS SPREAD TO THE BONES

Prostate cancer originates in the prostate gland but may spread to other tissues.[1] Testosterone, an androgen hormone, enhances the growth and spread of prostate cancer cells; therefore, one of the earliest types of treatment for prostate cancer is hormonal therapy that lowers testosterone levels.[2]

Hormone therapy can help shrink or slow the growth of prostate cancer.[2] If you are diagnosed with prostate cancer that no longer responds to medical or surgical treatments that lower testosterone, your healthcare team will conduct tests to find out whether the disease has spread beyond the prostate gland (or metastasized).[3] Bone is the most common site of metastasis in patients with prostate cancer and bone metastases impact nearly 90% of men with CRPC.[4,5]

Bone metastases can cause increased risk of death.[6-8] They may be associated with symptoms, but "very few patients are able to attribute their symptoms, when they first start, to their cancer…they're not thinking of the symptoms as cancer," says Oliver Sartor, MD, medical director at the Tulane Cancer Center in New Orleans, LA. Your healthcare team will consider evaluating you for symptomatic bone metastases if you are experiencing weakness, problems with your posture, difficulty moving, or pain creating the need for pain medications, including those that are over-the-counter.[9,10] Be sure to talk with your healthcare team about symptoms you experience; it's important to know that this includes any *new* symptoms and changes in symptoms, too.[9-11]

If symptoms suggest that prostate cancer has spread to your bones, your healthcare team will talk with you about ways to treat it. Taking time to learn about your treatment options and asking questions about things that are unclear may help you to understand what to expect before, during, and after treatment. Frequent conversations with your healthcare team will help you to make more informed decisions.[1,12,13] There are treatments available that may help slow the spread of your cancer.

Until recently, the only treatment option for metastatic CRPC that improved the chances of living longer was chemotherapy. Fortunately, in the last several years, treatment options have been approved that prolong life in patients with metastatic prostate cancer.[14-19] Different considerations come into play when deciding on a treatment, including short- and long-term side effects, the chances of living longer (with or without treatment), age, general health, and personal preferences. The healthcare team works together to create an overall treatment plan.[12]

Creating a treatment plan involves considering the risks and benefits of available treatments.[12] One of the available treatment options, approved May 15, 2013, is Xofigo® (radium Ra 223 dichloride) injection.[19] Xofigo (pronounced zo-FEE-go) is a radiopharmaceutical treatment approved by the US Food and Drug Administration.[19] It is an option for patients with prostate cancer that is resistant to medical or surgical treatments that lower testosterone and has spread to their bones with symptoms, but not to other parts of the body.[19]

Radium is an alkaline earth metal, discovered by Marie and Pierre Curie in 1898.[20] Radium and calcium have similar chemical properties, so radium predominantly accumulates in areas in your bones that are growing quickly, just like calcium does. Bone metastases are one of those rapidly growing areas,[21-23] which is why doctors use Xofigo to treat prostate cancer that has spread to the bones. Xofigo gives off a strong energy that helps kill cancer cells but limits damage to nearby healthy cells and tissue.[19,24] Xofigo can be absorbed by organs other than the bone, primarily the bone marrow and digestive system, which can result in side effects in those healthy tissues.[19] Before beginning any treatment for CRPC that has spread to the bones, including Xofigo, it can be helpful to talk with the healthcare team about possible side effects.[19]

In the ALSYMPCA clinical trial, 921 men with prostate cancer who had at least two bone metastases with symptoms and no known tissue metastases were given either Xofigo or placebo by injection.[25] In both of these groups, the men were also taking other medications for their disease.[25]

The results of ALSYMPCA showed that the men who received Xofigo lived significantly longer; they had a median overall survival of 14.9 months vs 11.3 months in the group of placebo-treated men in an updated analysis.[25] The survival results of ALSYMPCA were supported by a delay in their first bone-related symptom or event (called "symptomatic skeletal events"), favoring patients who were on Xofigo. Most of the events were external beam radiation therapy (treatment using a focused beam of radiation delivered from a device external to the body) to cancer spread to the bones.[25]

Dr. Sartor notes, "I believe Xofigo is a valuable addition to the available treatment options for patients."

Before beginning any treatment for CRPC that has spread to the bones, including Xofigo, you should talk with the healthcare team about possible side effects.[19] Do not take Xofigo if you are pregnant or may become pregnant. Xofigo can harm your unborn baby. Women who are pregnant or who may become pregnant should not come in contact with Xofigo without protection, such as gloves. Before taking Xofigo, tell your healthcare provider if you have bone marrow problems. Xofigo can cause your blood cells counts to go down, including red blood cells, white blood cells, and/or platelets. In a clinical trial, some patients had to permanently discontinue therapy because of bone marrow problems. In addition, there were some deaths and blood transfusions that occurred due to severe bone marrow problems. Your healthcare provider will do blood tests before and during treatment with Xofigo. Also tell your healthcare provider if you are receiving any chemotherapy or another extensive radiation therapy or have any other medical conditions.

<u>While you are on Xofigo</u>:

Make sure you keep your blood cell count monitoring appointments and tell your healthcare provider about any symptoms or signs of low blood cell counts. Report symptoms or signs of shortness of breath, tiredness, bleeding (such as bruising), or infection (such as fever). Stay well hydrated and report any signs of dehydration (such as dry mouth and increased thirst), or urinary or kidney problems (such as burning when urinating). There are no restrictions regarding contact with other people after receiving Xofigo. Follow good hygiene practices in order to minimize radiation exposure from spills of bodily fluids to household members and caregivers for a period of one week after each injection. Use condoms and make sure female partners who may become pregnant use highly effective birth control methods during and for a minimum of six months after treatment with Xofigo. The most common side effects of Xofigo include: nausea, diarrhea, vomiting, swelling of the arms or legs (peripheral edema), and low blood cell counts.

Tell your healthcare provider if you have any side effects that bother you or do not go away.[26]

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A TREATMENT OPTION FOR ADVANCED PROSTATE CANCER *(Continued from page 4)*

If Xofigo® (radium Ra 223 dichloride) is right for you, your healthcare provider will refer you to a clinic or facility where healthcare providers or technicians are qualified to give Xofigo.[19] Over the course of your therapy, you will get a total of six intravenous injections of Xofigo—one injection every four weeks. The injection of Xofigo will be given over one minute.[19,25]

If you have CRPC, it's important for you—and those who care for you—to learn about your cancer care and all of your treatment options. Talk with your healthcare team about symptoms you are experiencing and your treatment plan.[1] If you have prostate cancer that has spread to your bones, you may want to ask about Xofigo.[19]

Xofigo is available by prescription only.

To learn more about Xofigo, speak to your clinician and visit http://xofigo-us.com/patient/.

Please see full Prescribing Information at http://www.xofigo-us.com/product-information/.

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WEAREVER INCONTINENCE BRIEFS

We're pleased to be partnering with Wearever men's incontinence briefs. Throughout the month of September, 10 percent of all proceeds will be donated to Us TOO.

Incontinence can be a common side effect from some prostate cancer treatments. Classic incontinence briefs and incontinence Boxer Briefs by Wearever provide another option for dealing with a little leakage. In addition to being washable and reusable, they look and feel more like regular underwear while providing a comfortable fit and absorbent protection that wicks moisture away from the body. Wearever's incontinence briefs are constructed with sewn-in Unique-Dri™ pads and odor eliminating Agion™ antimicrobial fibers. And since each brief or boxer brief should last for 200 to 250 washes, they are more economical than disposables. Find out more at www.weareverincontinence.com.

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DOCS DRIVE TREATMENT CHOICE

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Physician characteristics were determined from the American Medical Association Physician Masterfile. The authors developed statistical models to evaluate variation in clinical management and identify factors associated with observation. The primary outcome was absence of cancer-directed therapy during the first 12 months after diagnosis.

The analysis included 12,068 men and 2,145 urologists. Overall, 80.1% of men received upfront therapy, and 19.9% began observation. The case-adjusted rate of observation by diagnosing urologist varied almost 15-fold from the lowest (4.5%) to highest (64.2%) proportion of patients managed by observation.

Analysis of factors that affected variation in the use of observation showed that the diagnosing urologist accounted for 16.1% of the variation compared with 7.9% for patient and disease characteristics.

After adjustment for patient and tumor characteristics, the probability that a patient would be observed was 29% lower if the diagnosing urologist treated non-low-risk prostate cancer (adjusted odds ratio 0.71, 95% CI 0.55-0.92, P=0.01).

Men who saw only a urologist were significantly more likely to be observed than were men who were seen by a urologist and a radiation oncologist (43.8% versus 8.6%, P <0.001). Authors found that 70.8% of men observed saw only a urologist. Men older than age 70 and with clinical T2 disease at diagnosis were significantly more likely to be observed (P <0.001). However, 55.1% of men older than 80 underwent upfront definitive treatment. Comorbidity score and PSA level did not significantly affect the likelihood of observation.

"We weren't necessarily surprised by the findings, but the extent of variation in management of low-risk prostate cancer across physicians was quite striking," Hoffman told MedPage Today.

"The evidence of substantial variation in the approach to treatment means that patients with low-risk prostate cancer should take the initiative to ask whether they are candidates for observation," she added. Public reporting of the data will allow primary care physicians to seek out urologists who are inclined to recommend observation for low-risk cases.

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RESULTS OF COMET-1

(Continued from page 1)

the investigators is the only time-to-event-based endpoint for which data are available. Median PFS was 5.5 months for the cabozantinib arm of the trial versus 2.8 months for the prednisone arm (hazard ratio 0.50; 95% CI 0.42–0.60; p <0.0001). Safety data were consistent with those observed in earlier-stage trials of cabozantinib in mCRPC.

As a result of the outcome of COMET-1, Exelixis will initiate a significant workforce reduction to enable the company to focus its financial resources on the late-stage clinical trials of cabozantinib in metastatic renal cell carcinoma (the METEOR trial) and advanced hepatocellular carcinoma (the CELESTIAL trial). The company will reduce its workforce by approximately 70 percent, or approximately 160 employees, resulting in approximately 70 remaining employees.

"We are very disappointed that COMET-1 did not meet its primary endpoint of extending overall survival in men with mCRPC," said Michael M. Morrissey, PhD, president and chief executive officer of Exelixis. "We are grateful to the patients, physicians, nurses, caregivers, and other study team members who participated in the trial."

Dr. Morrissey continued, "We have thoughtfully prepared for this scenario and the resulting very difficult decisions. The workforce reduction we have announced today is necessary to significantly reduce our corporate operating expenses. I would like to personally express my deep appreciation to the talented and dedicated Exelixis employees who will be impacted by these actions, both for their commitment to Exelixis and for their tremendous contributions to patients with cancer."

Based on the outcome of COMET-1, Exelixis has deprioritized the clinical development of cabozantinib in mCRPC. Enrollment in COMET-2, which is the second pivotal trial in mCRPC and evaluates pain palliation, has been halted. The company expects top-line data before the end of this year. Based on the outcome of COMET-2, Exelixis will discuss with regulatory authorities the potential regulatory path, if any, of cabozantinib in mCRPC. Other company-sponsored studies in mCRPC, including a randomized phase 2 study of cabozantinib in combination with abiraterone, will also be halted.

FiercePharma.com, 2 September 2014

VARIATION IN TREATMENT ASSOCIATED WITH LIFE EXPECTANCY IN A POPULATION-BASED COHORT OF MEN WITH EARLY-STAGE PROSTATE CANCER

Daskivich TJ, Lai J, Dick AW, et al

Cancer 17 July 2014; Epub

Background: Men with major comorbidities are at risk for overtreatment of prostate cancer due to uncertainty regarding their life expectancy. We sought to characterize life expectancy and treatment in a population-based cohort of men with differing ages and comorbidity burdens at diagnosis.

Methods: We sampled 96,032 men aged ≥66 years with early-stage prostate cancer who had Gleason scores ≤7 and were diagnosed during 1991 to 2007 from the Surveillance, Epidemiology, and End Results-Medicare database. We calculated cumulative incidence of other-cause mortality and determined treatment patterns among subgroups defined by age and Charlson comorbidity index scores.

Results: Overall, life expectancy was <10 years (10-year other-cause mortality rate, >50%) for 50,049 of 96,032 men (52%). Life expectancy differed by age and comorbidity score and was <10 years for men ages 66 to 69 years with Charlson scores ≥2, for men ages 70 to 74 years with Charlson scores ≥1, and for all men ages 75 to 79 years and ≥80 years. Among those who had a life expectancy <10 years, treatment was aggressive (surgery, radiation, or brachytherapy) for 68% of men aged 66 to 69 years, 69% of men aged 70 to 74 years, 57% of men aged 75 to 79 years, and 24% of men aged ≥80 years. Among these men, aggressive treatment was predominantly radiation therapy (50%, 53%, 63%, and 69%, respectively) and less frequently was surgery (30%, 25%, 13%, and 9%, respectively). Multivariate models revealed little variation in the probability of aggressive treatment by comorbidity status within age subgroups despite substantial differences in mortality.

Conclusions: Men aged <80 years at diagnosis who have life expectancies <10 years often receive aggressive treatment for low-risk and intermediate-risk prostate cancer, mostly with radiation therapy.

DOCTOR CHODAK'S BOTTOM LINE *(Ref Key: article #, page #, column #)*

Gerald Chodak, MD Author, *Winning the Battle Against Prostate Cancer*, Second Edition http://www.prostatevideos.com

Editor's note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 As interest in active surveillance grows, newly diagnosed men should realize that their likelihood of having this treatment is dependent on factors beyond the characteristics of their tumor. The study by Hoffman and co-workers found that patients were significantly more likely to undergo local therapy if their doctor was a D.O., they were trained in certain time periods, or they saw both a urologist and a radiation therapist compared to a urologist alone. The treatment also was influenced by the treatments offered; patients whose doctor performed cryosurgery or brachytherapy were more likely to have one of those treatments than when their doctor did not perform them. Surprisingly, 55% of men over the age of 80 had local therapy. This should come as no surprise because presently doctors make their own decision regarding the information given to patients about treatment options. Unless or until some standardized information is made available to all patients, the biases of their doctor will greatly influence which treatment they receive. That places an added burden on all men and their families to carefully investigate the pros and cons of the various options.

The Bottom Line: As I have previously written in this column, men should specifically ask about the ***odds*** of the treatments helping them live longer or impairing their quality of life compared to active surveillance. One critique of this paper is that it only includes men treated up to 2009 and results may have changed significantly during the last five years.

a4p2c2 Choline PET scans are increasingly being used in the management of men with prostate cancer, although its true value still remains uncertain. One of the challenges is variability in the interpretation of the scans. In an effort to define this variability, Pegard, et al evaluated the results for four doctors evaluating scans in patients who had a biochemical recurrence following local therapy. They used the Fleiss' kappa coefficient to assess the variability between these doctors. This value ranges from 0 to 1, where 0 means there is no consistency and 1 means there is complete agreement. No one has determined what an acceptable value is. Here the authors report a Fleiss' kappa coefficient of 0.55, which seems like it is only a fair result. They found the weakest correlation in men with an intact prostate. Although the agreement was better for lymph node involvement, one might reasonably ask, "So what?" The only purpose for considering this test after radical prostatectomy is to determine if salvage radiation is worth doing and studies have shown limited benefit. Knowing that a patient has recurrence in the lymph nodes does little to help guide therapy because there is no known survival benefit from early ADT in these men. Another concern with the findings is the authors did not show how the PSA level might impact on the findings.

The Bottom Line: It would have been helpful to know the level of agreement at different PSA levels. Perhaps concordance is not very good unless the PSA is above a certain value. Nevertheless, this is a first attempt to demonstrate variability in interpreting PET scans and more work in this area is needed.

a5p2c3 One of the challenges facing men considering active surveillance is whether the prostate biopsy has adequately sampled the gland. In the United States, a 12-core biopsy has become the standard, but many doctors still do more than that number. Also, some doctors advise a repeat biopsy before advising active surveillance. A question that has not been resolved is whether doing more than 12 cores at the initial biopsy would enable men to avoid having to undergo a second biopsy. This has been partly addressed by Villa et al who correlated the number of biopsies with the findings at radical prostatectomy. Although they did find some correlation, a weakness of the paper is they combined all Gleason 7 cancers together, i.e., 3+4=7 and 4+3=7. The problem with this approach is many men with Gleason 3+4=7 are still considered candidates for active surveillance.

The Bottom Line: To really determine if patients would be better served by having more than a 12-core biopsy, the data would need to be re-analyzed by separating the patients with Gleason 7 tumors into the two groups.

a8p6c3 The article by Daskivitch et al provides further support for the overtreatment of men with low- or intermediate-risk disease. They looked at SEER data from 1991-2007 and correlated the likelihood of men over 65 getting treated based on their life expectancy. Obviously, doctors cannot predict with certainty the time when someone will die. All that can be done is to talk about percentages of men surviving for a defined number of years based on age and overall health. When choosing therapy, many patients expect their survival to be longer than what will actually occur. That might help explain why the authors found a significant percentage of men with life expectancies less than 10 years get local therapy. That means a large percentage of them are getting treated with almost no chance of benefitting.

The Bottom Line: Something seems wrong when 68% of all men with a life expectancy less than 10 years or 24% of men over 80 years of age are getting surgery, radiation, or brachytherapy. The message to patients is to ask your family doctor to give you some idea about your life expectancy based on your age and health status so you are in a better position to decide if the possible benefits of treatment really do outweigh the risks.

a10p8c1 As has been discussed in the past, significant progress has been made in managing castrate-resistant prostate cancer. In addition to sipuleucel-T (Provenge®), abiraterone acetate (Zytiga®), and radium Ra-223 dichloride (Xofigo®) being approved prior to docetaxel chemotherapy, the FDA just announced approval of enzalutamide (Xtandi®) for those same patients. All these agents improve survival. For those failing docetaxel/prednisone, cabazitaxel is also approved. Now comes the hard part; figuring out the best sequence, which is likely to vary among patients.

The Bottom Line: Until definitive studies are done, doctors are likely to have a variable approach. Cost and side effects are two factors that need to be considered. One question is whether administering sipuleucel-T is the best place to start in men with minimal or no symptoms and then proceeding on to either abiraterone/prednisone or enzalutamide. For those who do have significant bone pain, radium Ra-223 dichloride rather than sipuleucel-T seems most reasonable. Hopefully, definitive studies will be published soon to help patients and doctors make treatment decisions.

FDA APPROVES NEW USE OF XTANDI® CAPSULES FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Medivation, Inc. and Astellas Pharma Inc. announced that the US Food and Drug Administration (FDA) approved a new indication for the use of XTANDI® (enzalutamide) capsules to treat patients with metastatic castration-resistant prostate cancer (CRPC). This new approved use follows a priority review of the supplemental New Drug Application (sNDA) that was based on results of the Phase 3 PREVAIL trial.

The FDA initially approved XTANDI, an oral, once-daily androgen receptor inhibitor, in August 2012 for use in patients with metastatic CRPC who previously received docetaxel (chemotherapy). The new indication approves XTANDI for use in men with metastatic CRPC who have not received chemotherapy. Metastatic CRPC is defined as a cancer that has spread beyond the prostate gland and has progressed despite treatment to lower testosterone (i.e., with a gonadotropin-releasing hormone (GnRH) therapy or with removal of the testes). Enzalutamide is an androgen receptor inhibitor that acts on three different steps in the androgen receptor signaling pathway.

In the Phase 3 PREVAIL trial, men receiving XTANDI and GnRH therapy exhibited a statistically significant improvement in both overall survival and delayed time to radiographic progression or death as compared to those on placebo and GnRH therapy.

XTANDI significantly reduced the risk of radiographic progression or death by 83% compared with placebo (HR=0.17; p <0.0001). XTANDI significantly reduced the risk of death by 29% compared with placebo (HR=0.71; p <0.0001). When compared to placebo, treatment with XTANDI also delayed time to initiation of chemotherapy and time to a skeletal-related event.

The safety profile for XTANDI was updated to reflect data from both the AFFIRM and PREVAIL Phase 3 trials. Seizure occurred in 0.9% of patients receiving XTANDI who previously received docetaxel and 0.1% of patients who were chemotherapy-naive. The most common adverse reactions (≥10%) that occurred more commonly (≥2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

"All of us at Medivation extend our thanks to the clinicians and patients who participated in the PREVAIL clinical trial culminating in today's approval," said David Hung, MD, founder, president and chief executive officer, Medivation, Inc. "As a company dedicated to the rapid development of novel therapies to treat serious diseases, we are pleased to see XTANDI approved in this important patient population."

MarketWire, 10 September 2014

CHOLINE PET/CT

(Continued from page 2)

interpretation of (^{18}F) choline positron emission tomography/computed tomography examinations, which is a key examination for the treatment of patients suffering biochemical recurrence of prostate cancer. Interpretation of the (^{18}F) choline emission tomography/computed tomography examination is not so useful at prostate level in patients not previously treated with prostatectomy but has a great interest on patients treated by prostatectomy. It showed good concordance in the interpretation of sub-diaphragmatic lymphatic recurrences as well as in bone metastasis.

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