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Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

June 2009

UROLOGISTS SUPPORT BASELINE PSA TEST AT AGE 40

Going against the flow on PSA testing, which has been questioned as a general prostate cancer screen elsewhere, the American Urological Association now recommends that physicians start offering the test to men at age 40. The rationale for an earlier baseline test is that a PSA value above the median at a relatively young age portends an increased risk of prostate cancer, said Peter Carroll, MD, who chaired the AUA panel that developed the recommendation.

After a baseline measurement, subsequent PSA testing should be individualized to a man's risk profile. "The single most important message of this statement is that prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physicians and urologists," said Dr. Carroll, of the University of California San Francisco. "There is no single standard that applies to all men, nor should there be at this time."

"The bottom line about prostate cancer testing is that we cannot counsel patients about next steps for cancer that we do not know exists," he added.

The recommendations were in an up-

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DUTASTERIDE LOWERS RISK FOR PROSTATE CANCER

Results from the first-ever study of chemoprevention in prostate cancer show that dutasteride (Avodart®) lowers the risk for prostate cancer by a significant 23%, with risk for high-grade tumors reduced in particular, investigators reported at the 2009 AUA 104th Annual Scientific Meeting.

The Reduction by Dutasteride of Prostate Cancer (REDUCE) trial is a worldwide, 4-year, randomized placebo-controlled trial of 8200 men from 50 to 75 years with elevated PSA levels and a negative prostate biopsy at baseline. The median baseline PSA level was 5.9 ng/mL, (range 2.5 to 10.0 ng/mL). Patients were randomized to dutasteride, a dihydrotestosterone 5-α reductase inhibitor, 0.5 mg daily, or placebo. PSA levels were measured biennially for 4 years, and prostate biopsies were conducted at 2 and 4 years.

"After 4 years, there was an absolute risk reduction of 22.5% and a relative risk reduction of 23%," Dr. Andriole announced. There were 659 cases of prostate cancer in the dutasteride group and 857 cases in the placebo group. The incidence of cancer by year 2 was 13.4% with dutasteride and 17.2% with placebo. By year 4, the

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PROSTATE CANCER VACCINE SIGNIFICANTLY IMPROVES 3-YEAR SURVIVAL

Phase 3 results from the Immunotherapy for Prostate AdenoCarcinoma Treatment (IMPACT) study, presented at the AUA 104th Annual Scientific Meeting, showed that prostate cancer immunotherapy with sipuleucel-T (Provenge®, Dendreon Corp.) extended median survival by 4.1 months and improved 4-year survival by 38%.

Results from the IMPACT study were presented by David F. Penson, MD, MPH, professor of medicine at the University of Southern California at Los Angeles. The study involved 512 men with minimally or asymptomatic metastatic castrate-resistant prostate cancer who were randomized in a 2:1 fashion to sipuleucel-T or placebo.

The vaccine was manufactured from the patient's leukocytes, which were expanded over a 2- or 3-day period and then re-infused on day 3 or 4 on an outpatient basis. Three cycles were given over the course of a month.

Sipuleucel-T extended median survival by 4.1 months; median survival was 25.8 months with active treatment and

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WEBSITE: WWW.USTOO.ORG

LIVING AND LOVING WITH PROSTATE CANCER: MEN DESERVE BETTER

Treat the disease and the man, urge advocacy groups worldwide.

Vast improvements in prostate cancer recognition, management and treatment are needed, according to influential prostate cancer groups, speaking today on the occasion of the American Urological Association annual meeting. In particular, a Charter for Change called Learning, Living and Loving draws attention to the impact of prostate cancer on a man's love life which can be affected due to changes in his sexual function, and changes in the way he perceives his own masculinity.

The charter from 13 major prostate cancer groups in the US and Europe calls on policy makers, patient groups, healthcare professionals, pharmaceutical companies, the media and the public to advance the early detection, diagnosis, treatment and management of prostate cancer, and take effective steps to improve the handling of the 'whole man' - mind, body and spirit.

"Prostate cancer is reaching epidemic status. It is possibly one of the biggest challenges to men's health in the world today but through the charter, we're urging men to take control of their own healthcare." comments Thomas Kirk, President and CEO of Us TOO International Prostate Cancer Education and Support Network. "Men should put their best healthcare team on the field. That's to say they should assemble the best team of doctors and researchers around them for advice on treatment options, and draw strength from the loving support of their family, to help them manage the impact the disease can have on how they feel emotionally, on their love life and on their feelings of intimacy with their partner."

The group's overarching concern is a lack of clear and consistent information, particularly in areas affecting men's quality of life and of his family. Prostate cancer and its treatments impact on all elements of a man's life. Many men experience urinary incontinence and impotence, and a loss of sexual desire which can severely compromise their sense of masculinity and affect their work, social activity and love life. The charter asks for practices to be put into place to better inform and educate men, their families and all those involved in prostate cancer care of the far reaching effects of the disease and to encourage a more open, communicative and holistic approach to its treatment and management.

Skip Lockwood, Executive Vice President and CEO of ZERO explains, "There is still much to be done to improve the management of prostate cancer and the fight against the disease is far from over. Prostate cancer does not receive anywhere near the level of interest and funding it warrants and this must be addressed. Our charter highlights the shortcomings in the current management of men with this disease but from a very practical viewpoint. For example, maintaining key relationships, love life and intimacy throughout prostate cancer is incredibly important but can often be overlooked. Many men feel uncomfortable discussing these issues and avoid them

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US TOO SEEKS BOARD MEMBER APPLICATIONS

Us TOO is pleased to announce the annual public call for nominations to the Us TOO International Board of Directors. The Board Membership Committee, chaired by Carl Frankel, will review and evaluate nominees and submit recommendations to the full Board for approval at its December 2009 Board meeting.

Selection criteria includes items such as the candidate's relationship to Us TOO's purpose, its membership criteria ("…any man diagnosed with prostate cancer, a member of such a man's family or significant other, or any person involved in or interested in support or treatment of any such patients…"), familiarity with an Us TOO chapter, ability to think globally, skills or experience deemed beneficial to the work of Us TOO and commitment to Us TOO's purpose and mission.

Letters of nomination with a vita or resume should be sent by August 31, 2009 to Thomas Kirk, President/CEO, Us TOO International, 5003 Fairview Avenue, Downers Grove, IL 60515 or e-mail tom@ustoo.org.

STATINS MAY PROTECT PROSTATE HEALTH

Statins, drugs widely prescribed to lower cholesterol, may have protective effects on prostate health. This large Mayo Clinic cohort study looked at three different aspects of urological health – prostate cancer, erectile dysfunction, and prostate enlargement. These Mayo Clinic study findings came from data in the Olmsted County Study of Urinary Health Status among Men, a large cohort study of men living in Olmsted County, MN. This study has followed 2,447 men ages 40 to 79 from 1990 to the present to assess various urologic outcomes among aging men.

In the first study, researchers followed the 2,447 men for over 15 years. Of the statin users, 38 (6 percent) were diagnosed with prostate cancer; non-statin users were three times more likely to develop prostate cancer, suggesting statin use may prevent development of prostate cancer.

"In recent years, it has been suggested that statin medications may prevent development of cancer. However, until now, there has been limited evidence to support this theory," says Rodney Breau, MD, a Mayo Clinic urologic oncology fellow who led the study. "Our research provides evidence that statin use is associated with a threefold reduced risk of being diagnosed with prostate cancer."

"In the United States, one in six men will develop prostate cancer; however, far more will develop heart disease," says Jeffrey Karnes, MD, Mayo Clinic urologist and senior author on the study. "I tell my patients to take care of their heart – because what's good for the heart is also good for the prostate," says Dr. Karnes.

With this in mind, a second study by Mayo Clinic researchers evaluated 1,480 men from the Olmsted County cohort to determine if men who used statins were less likely to develop erectile dysfunction (ED), compared to men who did not use statins. Hyperlipidemia, high cholesterol, and other risk factors for heart disease have been shown to put men at risk for ED.

Overall, statin use was not significantly associated with a decreased risk of developing ED. However, statins were associated with a decreased risk of ED among men >60 years old. Men in this age category using statins were less likely to develop ED, compared to older men who did not use statins.

Additionally, men who took statins for a longer time were more protected against developing ED. For example, men who took statins for nine or more years were 64 percent less likely to develop ED, while men who took statins for less than three years had about the same risk of developing ED compared to men who did not take statins.

"Protection of vascular health remains an important concomitant of preserving erectile health. Our data suggest that longer use of statins may result in the lowest risk of erectile dysfunction," says Ajay Nehra, MD, Mayo Clinic urologist and senior study author. ED is common and prevalence increases with age. At age 40, it affects five to 10 percent of men but this increases to 40 to 60 percent at age 70.

The third study focused on benign prostatic enlargement, or hypertrophy. This condition affects one in four men ages 40 to 50 and almost half of 70- to 80-year-old men. The condition is most often diagnosed when men visit their physicians due to urinary problems prompted by prostate enlargement.

Mayo Clinic researchers have found that taking statins may prevent or delay benign prostatic enlargement. Of the 2,447 men studied, 729 (30 percent) were statin users; researchers found that statin users were 63 percent less likely to develop lower urinary tract problems and 57 percent less likely to develop an enlarged prostate.

"Statins have been shown to have anti-inflammatory effects, and previous research suggests inflammation may be associated with benign prostate disease," says Dr. Jennifer St. Sauver. epidemiologist at the Mayo Clinic and study author. "This study suggests that men's urinary health could be improved by taking statin medications."

The investigators emphasize that these results are preliminary and that clinical trials are necessary to determine if taking statins might prevent development of these common conditions.

Mayo Clinic, 26 April 2009

RACE MAY NOT BE KEY IN CANCER DISPARITIES

Race and genetics may not be as big a factor in surviving certain cancers as long suspected, a new study finds. Researchers say they are far less apparent when zeroing in on smaller geographical areas, such as a neighborhood.

A report in the May 15th issue of the journal *Cancer* suggests that this means that modifiable factors – such as socioeconomic situations, stages of the cancer, treatment and other aspects of a person's health – might play a bigger role than biology in determining survival from a tumor.

In the report, led by Jaymie Meliker, an assistant professor of preventive medicine at Stony Brook University in New York, NY researchers reevaluated information that whites in southern Michigan had far better survival rates than blacks when diagnosed with breast or prostate cancer. The gaps often were negligible – and sometimes completely disappeared -- when the population or geographic focus narrowed from large counties to just cities, towns or neighborhoods.

The study did not delve into the relative impact of different modifiable factors but did suggest that genetic factors probably were not key determinants in survival differences.

For more information, go to <http://seer.cancer.gov/publications/survival/surv_race_ethnicity.pdf>.

HealthDay News, 13 April 2009

DON'T FORGET JUNE 2009 US TOO ONLINE AUCTION

Support Us TOO's important mission of empowering men and their families battling prostate cancer!

The 4th Annual Us TOO Online Auction is June 8 -23, 2009.

Visit <www.ustoo.org> to donate or bid on great gifts!

GENETIC VARIANT ASSOCIATED WITH AGGRESSIVE PROSTATE CANCER

One of the biggest issues in prostate cancer is differentiating between men who have aggressive tumors that could be fatal and men who have indolent tumors that might never become clinically significant. At the 2009 American Association for Cancer Research (AACR) meeting , researchers reporting a new genetic variant associated with aggressive prostate cancer say it could be useful in differentiating between these 2 groups of patients.

The genetic variant is detected from a blood sample, and it shows a person's predisposition to aggressive prostate cancer, lead author John Wittle, PhD, from the Institute of Human Genetics at the University of California at San Francisco, told Medscape Oncology.

It was found in a case–control study involving 947 men with aggressive prostate cancer and 534 controls, and is located on the KIAA1217 gene, which has recently been reported to be a novel target for repression of the androgen receptor. This is the first time this has been found, so it needs validation, Dr. Whittle emphasized. Other groups are working to replicate the finding. If it is validated, it could be very important, he said.

The group is now working on a prediction model, in which information on this genetic variant is added to the clinical data that are already used – PSA levels, Gleason score, and tumor staging – to see if it can improve accuracy. The hope is that it will, and that it will enable clinicians to identify with more certainty men who are likely to have aggressive disease. This could result in less overtreatment, Dr. Wittle said, because clinicians will be able to identify tumors that will not cause problems.

Because the marker identifies a predisposition for aggressive disease, it could also be useful in prostate cancer screening, Dr. Wittle noted, because it would identify those who could benefit from more frequent screening.

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AGENT ORANGE INCREASES AGGRESSIVENESS OF RECURRENT PROSTATE CANCER

Veterans exposed to Agent Orange are at increased risk of aggressive recurrence of prostate cancer, researchers report.

A study of 1,495 veterans who underwent radical prostatectomy to remove their cancerous prostates showed that the 206 exposed to Agent Orange had nearly a 50 percent increased risk of their cancer recurring despite the fact that their cancer seemed relatively nonaggressive at the time of surgery.

Increasing evidence is emerging that exposure to Agent Orange, a defoliant used during the Vietnam War, increases risk for a variety of health problems, including prostate cancer, although the exact mechanism is unclear.

Dr. Martha Terris, chief of urology at the Charlie Norwood VA Medical Center in Augusta, GA and professor of urology at the Medical College of Georgia School of Medicine Terris was the corresponding author on the study published in the May 2009 issue of *BJU International*.

Dr. Terris led a separate study of 1,653 veterans at VA medical centers in Augusta, GA, Los Angeles, CA, Palo Alto, CA and six affiliated medical schools between 1990 and 2006 that also showed higher recurrence rates and more aggressive recurring cancers with Agent Orange exposure. This study included new patients as well as many of her original study patients after longer follow-up. Dr. Sagar R. Shah, MCG urology resident, presented the findings at the 2007 annual meeting of the American Urological Association.

Plenty of questions remain, such as what happens to patients whose primary treatment is standard radiation or brachytherapy, where rice-size radiation pellets are implanted in the prostate, rather than surgery, Dr. Terris said.

"There is something about the biology of these cancers associated with prior Agent Orange exposure that is causing them to be more aggressive. We need to get the word out," Terris added.

Science Daily News, 20 April 2009

NATIONAL CANCER INSTITUTE'S PLAN TO ACCELERATE CANCER RESEARCH ANNOUNCED

At the 2009 AACR meeting in Denver, Co National Cancer Institute (NCI) Director John E. Niederhuber, MD, announced major details, such as funding more grants, development of a platform for personalized cancer care, and an accelerated cancer genetics program, that will move cancer research forward in this new economic environment. NCI is part of the National Institutes of Health (NIH).

After several years of flat budgets or those that decreased based on rates of medical inflation, NCI received a nearly three percent budget increase this fiscal year. NCI's actions today follow on what President Barack Obama said recently when he announced the Obama-Biden Cancer Plan: "I hope this investment will ignite our imagination once more, spurring new discoveries and breakthroughs in science, in medicine, in energy, to make our economy stronger and our nation more secure and our planet safer for our children."

Among plans to strengthen cancer research discussed by Niederhuber include the following:

- An increase in the NCI payline to fund meritorious research projects
- More grants to 1st-time investigators
- Help to universities to assist and train new faculty investigators
- Develop personalized cancer care encompassing drug development, from discovery of genetic changes to clinical applications for patients
- Start a new network of Physical Sciences-Oncology Centers to better control cancer
- Expand the Cancer Genome Atlas to accelerate our understanding of the molecular basis of cancer

"We must hasten our progress against cancer by conducting exciting new science, which this year's increase in funding, in addition to anticipated funds from the American Recovery and Reinvestment Act (ARRA), will help make possible," said Niederhuber.

NCI Press Office, 20 April 2009

BASELINE PSA TESTING

(Continued from page 1)

date to the AUA Best Practice Statement on PSA testing, originally released in 2000. They were a significant departure from other organizations' recent recommendations on PSA testing.

For example, the American Cancer Society no longer recommends PSA testing at any age rather encourages men to ask about the risks and benefits of PSA testing with their physicians – including potential for unnecessary treatment – and then make the decision that best suits their situation. Also, the US Preventive Services Task Force concluded that "current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75." The task force recommended against PSA screening for prostate cancer in men 75 or older.

Posted on the AUA website, the latest practice statement does not set a specific PSA threshold to trigger a prostate biopsy. To support that position, the AUA panel drew from results of the Prostate Cancer Prevention Trial, which showed that prostate cancer may occur at any PSA level (termed a "continuum of risk)." Current methods combining a specific PSA threshold and digital rectal exam (DRE), can overestimate prostate cancer risk in some cases and underestimate in others.

"The decision to proceed to prostate biopsy should be based primarily on PSA and DRE results but should take into account multiple factors, including free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history, and comorbidities," the panel said in the practice statement.

The AUA panel's deliberations included consideration of two recent prostate cancer screening studies that produced disparate results. A US study showed no survival benefit with regular PSA screening, whereas a much larger European study showed a 20% to 27% reduction in prostate cancer mortality in men who were screened regularly. The AUA practice statement includes a review of both studies.

MedPage Today, 29 April 2009

DUTASTERIDE PREVENTION

(Continued from page 1)

incidence was 9.1% with dutasteride and 11.8% with placebo.

"It could be that dutasteride shrinks the prostate and thereby shrinks the tumors, but it also appears that dutasteride has an effect in high-grade tumor cells in particular, through both type 1 and type 2 5α reductase inhibitors," Dr. Andriole said. Type 1 receptor inhibition has a pronounced effect in high-grade tumor cells. Finasteride acts only on type 2 5α reductase inhibitors.

"Isn't it possible that the PSA doesn't rise until the prostate is filled with high-grade cells, making the cancer more difficult to treat at that point?" asked William J. Catalona, MD, from the Department of Urology at Northwestern Feinberg School of Medicine in Chicago, IL. "I understand the concern, but happily, the data do not support that," Dr. Andriole responded.

"Hormonal therapy is never curative," Dr. Catalona pointed out. "How long will the effects of dutasteride last?" Dr. Andriole agreed that the drug's effects will not be permanent. He emphasized that there was no increase in the incidence of high-grade tumors, "and these tumors with Gleason scores of 8, 9, and 10 are killers," he said. "In addition, dutasteride enhances the ability of PSA [testing] to detect cancers. It makes PSA a better test," he asserted.

"I would recommend chemoprevention for high-risk men based on these results. It is certainly enough to convince me. I would take it," Dr. Andriole stated. "Any man who is at high-risk because of age, rectal exam, and PSA level – or has other factors, such as a high [body mass index], a family history, or other reasons for a risk of prostate cancer greater than 30% in the next 4 years is a candidate in my book."

REDUCE was funded by GlaxoSmithKline, the maker of Avodart. Dr. Catalona has disclosed no relevant financial relationships.

Presented at the 2009 AUA 104th Annual Scientific Meeting, Late Breaking Abstract 1: partial results presented 27 April 2009; full results presented 28 April 2009.

Medscape Medical News, 28 April 2009

MEN DESERVE BETTER

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altogether. It is an area which is absolutely key to men's quality of life and there needs to be a cultural shift in the way it is approached and managed."

The prostate gland is part of the male reproductive system, and the growth and function of the prostate depends on the male sex hormone testosterone. In men, testosterone helps maintain sex drive and sexual function, muscle mass and strength, mood and energy levels as well as bone strength. Prostate cancer and some treatments can affect a man's natural hormone production and often trigger a number of side effects that impact the man's sex life, and consequently, that of his partner.

Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity – *World Health Organization*

Participating Prostate Cancer Groups

USA
Us TOO International Prostate Cancer Education and Support Network

ZERO – The Project to End Prostate Cancer

Austria
Selbsthilfe Prostatakrebs

Belgium
Wij Ook Belgie – Us TOO Belgium

Denmark
PROPA Prostate Cancer Patient Society

France
Association National des Malades du cancer de la prostate (l'ANAMACaP)

Germany
Bundesverband ProstataKrebs Selbsthilfe BPS

Ireland
Men Against Cancer (MAC)

Italy
Europa Uomo Italia Onlus

Netherlands
Stichting Contactgroep Prostaatkanker

Spain
FEFOC

Sweden
Prostatacancerforbundet

UK
Prostate Cancer Support Federation

The creation of the charter was funded by Ferring Pharmaceuticals

PR Newswire, 28 April 2009

PROVENGE

(Continued from page 1)

21.7 months with placebo. Three-year survival was improved by 38% compared with placebo (31.7% vs 23.0%).

"This 4-month extension in survival is very, very significant," Dr. Penson told Medscape Urology. "These patients have a life expectancy of about 2 years, so giving them 4 more months is pretty important. It gives them about 20% more life. And [sipuleucel-T] does it with minimal adverse events. So there is improved survival with good quality of life."

Treatments were extremely well tolerated, with chills reported in 54.1% of patients (vs 12.5% with placebo), fever in 29.3% (vs 13.7%), headache in 16.1% (vs 5%), and flu-like symptoms in 9.8% (vs 4.3%). Most adverse events lasted only a few days and were treatable with aspirin. "Some of our patients were golfing the day after treatment," Dr. Penson told reporters.

"The IMPACT study achieved a P value of 0.032, successfully exceeding the prespecified level of statistical significance," according to a Dendreon news release. Last year, the FDA deferred approval of sipuleucel-T until a statistically significant improvement in survival could be shown.

"The company and the FDA have to get back together to re-evaluate the results, but in my opinion, I think they should approve it" Dr. Penson added.

AUA spokesman J. Brantley Thrasher, MD, chair of the Department of Urology at the University of Kansas in Kansas City, KS, pointed out to Medscape Urology that "last year, the FDA put a damper on the approval process. They were looking for more survival data. This should give it to them."

"This will cause a big splash," Dr. Thrasher continued. "We don't have anything for patients with hormone-refractory disease, which is very aggressive. . . . Improved survival with T cell immunotherapy is really very significant."

Presented at the AUA 104th Annual Scientific Meeting: Late Breaking Abstract 9, 28 April 2009.

Medscape Medical News, 29 April 2009

THE DOCTORS NOTE

Dr. Gerald Chodak

The recent American Urological Association provided exciting new and in some cases controversial information about prostate cancer. Among the most controversial is the recent recommendation that all men should have a baseline PSA beginning at age 40.

That information should be used to formulate an individualized plan for each man. What makes this controversial is that two recent prospective randomized studies about screening demonstrated an extremely small benefit from screening men aged 55-74 and a very significant risk of over-treatment, at least at ten years. Those studies provide no insight as to whether testing men at an earlier age will offer a better outcome or potentially an even worse result with more over treatment.

The public ought to ask how this recommendation can be justified at this time. It also appears to be in conflict with recommendations by several other respected medical organizations. Although most men reading this column are likely to agree with this recommendation, the facts at this time do not support it. "Above all else, do no harm" is the credo that physicians agree to when completing medical training. It is quite reasonable to ask if this credo is being violated by this recommendation without scientific evidence to show it is correct.

In contrast, however, there were two very important presentations at the meeting that are likely to benefit men. The first was the results of the chemoprevention trial using dutasteride (Avodart®). Similar to the study with finasteride (Proscar®), this study also found a significant reduction in the incidence of prostate cancer.

The results have been presented to the public in an interesting way. Although there was a 23% reduction in the incidence of cancer, the public was not informed of the probability of benefiting from the treatment; in order to prevent one cancer, approximately 28 men would have to take the drug for four years. Men will have to decide if the size of this benefit is enough to pay for the medication for four years with a small incidence of side effects.

Also, what has not yet been determined is whether this reduction in incidence will translate into a reduction in the death rate from the disease which was not the design of the study. That information will be important to obtain in the future.

Another extremely important study was the latest update of the immunotherapy study using Sipuleucel-t (Provenge®). These results were necessitated by the FDA because previous studies did not provide enough evidence of benefit.

In this trial, survival of men with minimally or non-symptomatic metastatic disease improved median survival by 4.1 months. This compares closely with Taxotere® which had previously been shown to improve median survival by 2.1 months. Though not sizeable, these incremental improvements in survival further enhance the outlook for men with advanced disease.

It also offers an opportunity to look at the impact of these therapies in high risk patients even before metastases are present. An important aspect of this study is the ease of treatment and minimal side effect profile which is likely to make it easy for acceptance by many eligible men if and when the FDA provides its approval.

Yet another treatment with potential promise is a new drug by Medivation (MDV3100) that is an androgen receptor antagonist. The drug will enter phase III studies shortly. Its mechanism of action as well as that of another hormonal agent, Abiraterone, suggests that there is still more that can be accomplished with hormonal manipulation even in men who have had primary castration therapy. These study results, expected in the near future, will also be anxiously awaited .

Greater Chicago SEA BLUE PROSTATE CANCER WALK

September 13, 2009

ADT INCREASES RISK FOR FRACTURES AND CARDIOVASCULAR-RELATED DEATH IN PROSTATE CANCER PATIENTS

ADT (androgen deprivation therapy) is a common treatment for men with prostate cancer, but patients who do undergo this therapy are at an increased risk for skeletal fracture, incident diabetes, and cardiovascular-related mortality.

According to an analysis of 14 studies published online April 27th in the journal *Cancer*, patients who received ADT had a 23% increase in the risk for overall fracture and a 17% increase in cardiovascular-related mortality, compared with men who did not undergo treatment with ADT. Data from 2 large studies also indicated significant elevations in the risk for diabetes.

But lead author Lockwood G. Taylor, MPH, cautioned that although they did observe significant relative risks for skeletal fracture and cardiovascular-related death, the absolute risks for these adverse events are still very low.

To gain a better understanding of the magnitude of skeletal and cardiovascular adverse effects associated with ADT, Mr. Taylor and colleagues conducted a review that included summary risk estimates for specific outcomes. Their analysis examined 14 studies published from 1966 to 2008 that met their inclusion criteria.

Fracture Risk

There were 5 studies that investigated risk for fracture as a major adverse effect from ADT, 4 of which were retrospective cohort studies. The pooled results yielded a summary random-effects estimate of 1.23 (95% confidence interval [CI], 1.10 - 1.38) and a fixed-effects estimate of 1.17 (95% CI, 1.12 - 1.23).

In addition, 3 studies reported an increased risk for osteoporosis or lower bone mineral density in patients treated with ADT, compared with those who were not. In 2 studies that specifically evaluated osteoporosis as an outcome, there was an elevated association between ADT and osteoporosis, but only 1 of the studies found the risk to be statistically significant. The data also indicated that the duration of ADT is associated with osteoporosis and fracture risk; longer duration of ADT is associated with a higher risk.

Diabetes & Cardiovascular Morbidity

Of the 3 studies that investigated incident diabetes and other cardiovascular morbidity secondary to ADT treatment, all reported a significantly increased risk for diabetes or cardiovascular morbidity. The 3 studies were all retrospective cohort studies.

Two of the studies reported significantly increased risk for incident diabetes (between 36% and 49%), but the researchers caution that "further research beyond those 2 studies is needed to confirm the consistency and magnitude of the association."

ADT also increased the risk for cardiovascular morbidity, according to 1 paper in this subgroup. Patients who underwent treatment with ADT had a 20% increased risk for cardiovascular morbidity, compared with men who did not, and the duration of treatment was significantly associated with this risk.

Cardiovascular-Related Mortality

The authors also found that the results of studies investigating cardiovascular-related mortality secondary to ADT were relatively consistent. Of the 4 papers included in this analysis, 2 were retrospective cohort studies and 2 were randomized clinical trials.

The retrospective cohort studies both found significantly increased risks for cardiovascular-related mortality among patients who received ADT treatment, whereas the randomized trials reported slightly elevated but nonsignificant increases in cardiovascular-related mortality secondary to ADT.

The researchers point out that the absolute risk for cardiovascular-related mortality is low. Based on the assumption that the risk for cardiovascular-related mortality among men with prostate cancer who did not receive ADT is 9 or 10 deaths per 1000 person-years, they write, the observed 17% increase in relative risk would result in the increase of the absolute risk to 10.5 or 11.7 deaths per 1000 person-years, respectively, for men who underwent ADT.

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MEDIVATION PROSTATE DRUG SHOWS PROMISE

Medivation today announced publication of an article in the 9 April 2009 issue of *Science Express*, the online version of the journal *Science*, presenting the discovery and novel mechanism of action of MDV3100, the Company's androgen receptor antagonist drug candidate.

MDV3100 has completed enrollment in a Phase 1-2 study of a total of 140 men with CRPC. Patients in this trial were heavily pretreated, with all having failed standard hormonal therapies and many having also failed docetaxel-based chemotherapy. The drug is expected to enter Phase 3 development this year in metastatic castration-resistant prostate cancer (CRPC).

When testosterone binds to its natural receptor, the androgen receptor moves into the nucleus of the prostate cancer cell (nuclear translocation), binds DNA and stimulates prostate cancer growth. In CRPC, current anti-androgen therapies, despite binding to the androgen receptor, do not block nuclear translocation, which allows the receptor to bind to prostate cancer cell DNA and stimulate the tumor to grow.

In the *Science* article, researchers used various models of CRPC to provide evidence that MDV3100's novel mechanism of action is unlike that of the leading anti-androgen therapy bicalutamide. Specifically, MDV3100:

- Potently blocks the androgen receptor with greater binding affinity than bicalutamide
- Impairs nuclear translocation and blocks DNA binding of the androgen receptor, one of the key steps required for androgen-dependent prostate cancer growth and a step not blocked by bicalutamide and,
- Induces castration-resistant prostate tumor cell death, an effect not seen with bicalutamide

These properties potentially explain why MDV3100 has demonstrated beneficial effects in patients whose tumors are no longer responding to the currently available treatments for pros-

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AGGRESSIVE CANCER

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"This is a very interesting finding," said Eric Horwitz, MD, acting chair of radiation oncology at the Fox Chase Cancer Center, in Philadelphia, Pennsylvania. Dr. Horwitz specializes in treating prostate cancer, and was approached by Medscape Oncology for comment. The clinical factors that are currently used to predict whether a tumor is aggressive or not are "broad brush" and are sometimes not that accurate, he explained. PSA levels, in particular, can be unreliable; a patient with an aggressive tumor could have low levels, not the high levels that would be expected.

"A test that shows a genetic variant could fill in some of the pieces that are missing from the puzzle," Dr. Horwitz said, and "could potentially provide us with information to differentiate between patients." However, he cautioned that this work is still at the stage of basic research, and has not yet been tested in the clinic.

Presented at the 2009 AACR 100th Annual Meeting, Abstract 87, 19 April 2009.

Medscape Medical News, 22 April 2009

RISKS OF ADT

(Continued from page 7)

Preventive Steps Might Reduce Risk

Even though the absolute risks for fracture and cardiovascular mortality are low, preventive treatments could further reduce the risk for these potentially serious adverse events. "Preventive therapies to reduce these risks, such as lifestyle modifications or drug therapy, may be helpful, especially if the physician recognizes potential precursors to these adverse events, such as decreases in bone mineral density, an abnormal lipid profile, or a marked increase in body mass index," said Mr. Taylor.

The researchers also note that because some patients experience more benefit from ADT than others, physicians should consider each patient's overall health and prostate cancer status when weighing treatment options and a benefit–risk analysis must be considered.

"While the physician may wish to communicate these risks to the patient, it is imperative to convey that these risks are small in terms of minimal increase in absolute risk," said Mr. Taylor. "The benefits of ADT likely outweigh the risks"

Medscape Medical News, 30 April 2009

MDV3100

(Continued from page 7)

tate cancer, including bicalutamide.

"Because MDV3100 binds to the androgen receptor and blocks subsequent DNA binding, it can inhibit the growth of prostate cancer cells that have failed standard hormonal therapies and even chemotherapies," said Charles L. Sawyers, MD, lead author and chair of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center in New York, NY.

"I believe that MDV3100 is an important potential new approach to treating this disease and am encouraged that the drug is moving into Phase 3 clinical development."

"Publication of the MDV3100 manuscript in *Science* underscores the promise of this novel investigational drug., said David T. Hung, MD, president and chief executive officer of Medivation. "Given the encouraging results we have seen to date in our Phase 1-2 trial, we are pleased that we are on track to initiate patient enrollment in a Phase 3 trial of MDV3100 this year."

Company news release, 7 April 2009

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