US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

JUNE 2012

ANDROGEN DEPRIVATION IN ADVANCED PROSTATE CANCER NEEDN'T BE CONTINUOUS

When locally advanced or metastatic prostate cancer shows hormone sensitivity during induction androgen deprivation therapy (ADT), intermittent androgen deprivation (IAD) is a "feasible, efficient and safe" alternative to continuous androgen deprivation (CAD), Finnish clinicians report in the Journal of Urology (187: 2074-81, 2012).

In these patients, IAD did not carry a higher risk of death than CAD, Dr. Arto J. Salonen from Kuopio University Hospital and colleagues found. However, patients with the most advanced and the most aggressive prostate cancer are not candidates for IAD, they say. "PSA response for induction ADT is essential to determine patient eligibility for IAD (and for ADT, too)," Dr. Salonen said.

Between May 1997 and February 2003, 852 men with locally advanced or metastatic prostate cancer were recruited at 27 clinics in Finland to participate in the open label, randomized, controlled parallel group FinnProstate Study VII. All recruited patients received the luteinizing hormone releasing hormone (LHRH) analogue goserelin acetate (3.6 mg) subcutaneously every 28 days for 24 weeks (run in) before randomization. To minimize flare reaction, the antiandrogen cyproterone acetate was given in 100 mg

(Continued on page 3)

REVISED VIEW ENHANCES OVERALL SURVIVAL WITH PROVENGE

A further analysis of clinical trial data for sipuleucel-T (Provenge) suggests that the therapeutic prostate cancer vaccine may have delivered a greater overall survival (OS) benefit than previously described in the study that paved the way for its approval nearly two years ago, according to a leading researcher.

In fact, the analysis indicated that the survival benefit may be significantly higher than the 4.1-month advantage reported in the IMPACT study when the experiences of patients in the control arm who crossed over to a cryopreserved form of the vaccine are considered, said Leonard G. Gomella, MD, chairman of the Department of Urology and director of Clinical Affairs at the Kimmel Cancer Center, Thomas Jefferson University, in Philadelphia, PA.

Gomella discussed his hypothesis at the 5th Annual Interdisciplinary Prostate Cancer Congress (IPCC) 31 March 2012 in New York City, for which he served as a program director. The research was presented at the 2012 Genitourinary Cancer Symposium sponsored by the American Society of Clinical Oncology (ASCO) in February and at the 2011 ASCO Annual Meeting.[1]

Gomella's comments come amid continuing controversy over sipuleucel-T, including a recent commentary in the

(Continued on page 4)

STATS DON'T LIE: AVOIDING OVERTREATMENT OF PROSTATE CANCER

The most significant development in urology last year was the surprising recommendation from the US Preventive Services Task Force that routine PSA testing in healthy men is not indicated for early detection of prostate cancer. That draft recommendation has been soundly criticized in some circles and will probably be modified before it is finalized.

The rationale behind the recommendation, however, was the lack of randomized clinical trials showing that early detection leads to fewer cancer-specific deaths. Furthermore, early detection has led to overtreatment of patients with low-grade, low-risk cancer, in whom the side effects of prostate biopsy and subsequent treatment negatively outweigh the gain in cancer-specific survival, especially in elderly patients. Evidence of this disconnect was seen in the National Cancer Institute's Patterns of Care Study, which found that 71% of men older than 75 years with favorable-risk disease received radiotherapy. Only 12% were managed with active surveillance.

Of course, the good news is that most patients identified through early screening have curable, localized disease, and the mortality rate from prostate cancer has decreased 30%-40% in the PSA era.

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ROLE OF ISOTOPE SELECTION IN LONG TERM OUTCOMES WITH INTERMEDIATE-RISK PROSTATE CANCER TREATED WITH EXTERNAL BEAM RADIOTHERAPY AND LOW-DOSE-RATE INTERSTITIAL BRACHYTHERAPY

Wernicke AG, Shamis M, Yan W, et al

Urology 79(5): 1098-1104, May 2012

Objective: To examine the rates of long-term biochemical recurrence-free survival (BRFS) with respect to isotope in intermediate-risk prostate cancer treated with external beam radiotherapy (EBRT) and brachytherapy (BT).

Methods: A total of 242 consecutive patients with intermediate-risk prostate cancer were treated with iodine-125 (I-125) or palladium-103 (Pd-103) implants after EBRT (range 45.0-50.4 Gy) from 1996 to 2002. Of the 242 patients, 119 (49%) were treated with I-125 and 123 (51%) with Pd-103. Multivariate Cox regression analysis was used to analyze BRFS, defined according to the Phoenix definition (PSA nadir plus 2 ng/mL) with respect to Gleason score, stage, pretreatment PSA level, and source selection. Late genitourinary and gastrointestinal toxicities were assessed using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale.

Results: At a median follow-up of 10 years, the BRFS rate was 77.3%. A statistically significant difference was found in the 10-year BRFS rate between the I-125- and Pd-103-treated groups (82.7% and 70.6%, respectively; P = 0.001). The addition of hormonal therapy (HT) did not improve the 10-year BRFS rate (77.6%) compared with RT alone (77.1%; P = 0.22). However, a statistically significant difference in the BRFS rate was found with the addition of HT to Pd-103, improving the 10-year BRFS rate to 73.8% compared with Pd-103 alone (69.1%; P = 0.008). On multivariate analysis, isotope type (Pd-103 vs I-125), pretreatment PSA level >10 ng/mL, and greater tumor stage increased the risk of recurrence by 2.6-fold (P = 0.007), 5.9-fold (P <0.0001), and 1.7-fold (P = 0.14), respectively.

Conclusion: I-125 renders a superior rate of BRFS compared with Pd-103 when used with EBRT. HT does not provide additional benefit in intermediate-risk prostate cancer treated with a combination of EBRT and BT, except for the addition of HT to Pd-103.

FUNCTIONAL METABOLIC SCREEN IDENTIFIES 6-PHOSPHOFRUCTO-2-KINASE/FRUCTOSE-2,6-BIPHOSPHATASE 4 AS AN IMPORTANT REGULATOR OF PROSTATE CANCER CELL SURVIVAL

Ros S, Santos CR1, Sofia Moco S, et al

Cancer Discov 2: 328-343, 2012

Abstract: Alterations in metabolic activity contribute to the proliferation and survival of cancer cells. We investigated the effect of siRNA-mediated gene silencing of 222 metabolic enzymes, transporters, and regulators on the survival of 3 metastatic prostate cancer cell lines and a nonmalignant prostate epithelial cell line. This approach revealed significant complexity in the metabolic requirements of prostate cancer cells and identified several genes selectively required for their survival. Among these genes was 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4), an isoform of phosphofructokinase 2 (PFK2). We show that PFKFB4 is required to balance glycolytic activity and antioxidant production to maintain cellular redox balance in prostate cancer cells. Depletion of PFKFB4 inhibited tumor growth in a xenograft model, indicating that it is required under physiologic nutrient levels. PFKFB4 mRNA expression was also found to be greater in metastatic prostate cancer compared with primary tumors. Taken together, these results indicate that PFKFB4 is a potential target for the development of antineoplastic agents.

Significance: Cancer cells undergo several changes in their metabolism that promote growth and survival. Using an unbiased functional screen, we found that the glycolytic enzyme PFKFB4 is essential for prostate cancer cell survival by maintaining the balance between the use of glucose for energy generation and the synthesis of antioxidants. Targeting PFKFB4 may therefore present new therapeutic opportunities.

IADT IN ADVANCED PROSTATE CANCER *(Continued from page 1)*

twice daily during the first 12.5 days. The 554 patients in whom PSA decreased to less than 10 ng/mL or by 50% or more if less than 20 ng/mL at baseline were randomly allocated to IAD (274 patients) or CAD (280 patients).

"Patients with the most advanced and the most aggressive PC with high pretreatment PSA did not show adequate biochemical PSA response to ADT in our interim analysis and were not candidates for IAD (298 [35%] of 852 patients with advanced M0 or M1 PC)," Dr. Salonen stated. It was "surprising to some extent" that so many men were unsuitable for randomization, Dr. Salonen admitted, "because generally reported response rate for ADT in treatment of prostate cancer is approximately 80%."

In the CAD arm, patients continued with goserelin acetate or underwent bilateral orchiectomy. In the IAD arm, the LHRH analogue was withheld after randomization and was resumed, including flare protection with cyproterone acetate, for at least 24 weeks whenever PSA increased more than 20 ng/mL or above baseline and was withheld again by the same criteria as for randomization.

Of the 554 randomized patients, 392 (71%) died during a median followup of 65 months. There were 186 deaths in the IAD arm and 206 in the CAD arm (68% vs 74%; p=0.12). Prostate cancer was the cause of death in 248 cases - 117 in the IAD arm and 131 in the CAD arm (43% vs 47%; p=0.29).

The researchers report that median times from randomization to progression were longer, although not statistically so, in the IAD arm than the CAD arm (34.5 vs 30.2 months). There were no statistical differences in median times to death from any cause (45.2 and 45.7 months), to death from prostate cancer (45.2 and 44.3 months), and to treatment failure (29.9 and 30.5 months).

In Dr. Salonen's opinion, "IAD is a good option in treatment of advanced PC in patients whose prostate cancer shows hormone sensitivity during induction ADT." IAD "should be regarded as standard therapy for prostate cancer" in these patients, the study team concludes in their paper.

They also point out in the article that IAD offers economic benefit with the reduction of drug therapy costs during treatment off periods; however, patients on IAD need more careful followup while off therapy, which means extra costs to the health care system.

Reuters Health, 26 April 2012

NEW ERECTILE DYSFUNCTION DRUG OKAYED BY FDA

Avanafil (Stendra®, Vivus), a new drug to treat erectile dysfunction (ED), was recently approved by the US Food and Drug Administration (FDA). Three clinical trials involving 1267 patients established the safety and effectiveness of the new drug. Men were randomly assigned to take various doses of avanafil or a placebo for up to 12 weeks. Patients receiving avanafil reported significant gains in erectile function, vaginal penetration, and successful intercourse.

Avanafil belongs to the drug class called phosphodiesterase type 5 (PDE5) inhibitors, like Viagra, which increase blood flow to the penis. As a PDE5 inhibitor, avanafil should not be prescribed for men who also take nitrates, commonly used to treat angina, because the drug combination can cause blood pressure to decrease. In addition, FDA cautions that PDE5 inhibitors may cause an erection lasting 4 hours or more.

Avanafil is to be taken on as-needed basis 30 minutes before sexual activity. Clinicians should prescribe the lowest dose that works for an individual man.

The most common adverse events, reported in more than 2% of patients in the clinical trial, were headache, flushing, nasal congestion, and back pain.

Medscape Medical News, 27 April 2012

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SURVIVAL WITH PROVENGE

(Continued from page 1)

Journal of the National Cancer Institute that maintained previously unpublished data cast doubt on the vaccine's survival benefit partly because of factors involving patients in the placebo arm.[2]

FDA approved Provenge on 29 April 2010 for treating asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC) based on clinical trial data demonstrating that patients who took the vaccine experienced a median OS of 25.8 months versus 21.7 months for those receiving placebo. Sipuleucel-T is custom-made for each patient from antigen-presenting cells that are harvested from the patient through the process of leukapheresis, then cultured to activate immunogenicity, and infused into the patient. The treatment course consists of three intravenous infusions.

In his analysis, Gomella looked more closely at men in the control arms of three randomized, double-blind studies of sipuleucel-T. Of 249 men in the control arms, 216 with disease progression had the option of receiving APC8015F, an autologous immunotherapy with the same potency as sipuleucel-T that was made for each patient and cryopreserved at the time the placebo was prepared.

For the 155 patients from the control arm who received APC8015F, the median OS was 23.6 months from randomization and 20.0 months following disease progression, which compared favorably with the median OS in the sipuleucel-T arms of 25.4 months from randomization and 20.7 months after progression. In contrast, the 61 participants from the control arm who experienced disease progression but did not cross over to APC8015F had a median OS of 12.7 months from randomization and 9.8 months following disease progression.

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NUTRITION AND PHYSICAL ACTIVITY GUIDELINES FOR CANCER SURVIVORS

Rock CL, Doyle C, Demark-Wahnefried et al

CA Cancer J Clin 26 April 2012; Epub ahead of print

Abstract:

Cancer survivors are often highly motivated to seek information about food choices, physical activity, and dietary supplements to improve their treatment outcomes, quality of life, and overall survival. To address these concerns, the American Cancer Society (ACS) convened a group of experts in nutrition, physical activity, and cancer survivorship to evaluate the scientific evidence and best clinical practices related to optimal nutrition and physical activity after the diagnosis of cancer.

This report summarizes their findings and is intended to present health care providers with the best possible information with which to help cancer survivors and their families make informed choices related to nutrition and physical activity. The report discusses nutrition and physical activity guidelines during the continuum of cancer care, briefly highlighting important issues during cancer treatment and for patients with advanced cancer, but focusing largely on the needs of the population of individuals who are disease free or who have stable disease following their recovery from treatment. It also discusses select nutrition and physical activity issues such as body weight, food choices, food safety, and dietary supplements; issues related to selected cancer sites; and common questions about diet, physical activity, and cancer survivorship.

Editor's note:

These guidelines update a 2006 ACS report outlining the evidence on the impact of nutrition and physical activity on cancer recurrence and survival. Co-author Colleen Doyle, MS, RD, director of nutrition and physical activity at the ACS, stated, "While we've published previous reports outlining the evidence on the impact of nutrition and physical activity on cancer recurrence and survival, this is the first time the evidence has been strong enough to release formal guidelines for survivorship, as we've done for cancer prevention." The full report appeared 1 May 2012 in *Medscape Medical News.*

For the guidelines, a dozen experts in nutrition, physical activity, and cancer survivorship evaluated the scientific evidence and best clinical practices related to optimal nutrition and physical activity after the diagnosis of cancer.

One of the chief recommendations is to engage in regular physical activity. The aim should be at least 150 minutes per week of moderate-intensity activity and strength training twice a week. Since 2006, a number of studies have shown a reduction in the risk for cancer recurrence and an improved overall survival in breast, colorectal, prostate, and ovarian cancers. Exercise can also improve quality of life by reducing fatigue, psychosocial distress, depression, and low self-esteem among survivors.

One of the other main recommendations focuses on achieving and maintaining a healthy weight, defined as a body mass index from 18 to 25 kg/m². The authors note that there is "increasing evidence" that obesity is associated with an increased risk for cancer recurrence, and that it reduces the likelihood of disease-free and overall survival. After recovery from cancer treatment, intentional weight loss might be associated with health-related benefits, they explain. It is not proven that this will improve cancer-related outcomes, they note, but it is "likely probable."

The third main recommendation is to follow a diet rich in fruit, vegetables, and whole grains. Current US health recommendations are for adults to eat at least 2.0 to 3.0 cups of vegetables and 1.5 to 2.0 cups of fruit each day. Some studies suggest that omega 3 fatty acids have specific benefits for cancer survivors, such as ameliorating cachexia, improving quality of life, and enhancing some forms of treatment, but the findings are not entirely consistent. Nevertheless, foods that are rich in omega 3 fatty acids (including fish and walnuts) should be encouraged, the authors note, because they have been associated with reductions in cardiovascular risk and overall mortality.

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ASK DOCTOR SNUFFY MYERS

Editors' 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.

At age 52, I developed symptoms of prostatitis and difficulty urinating and went to see a urologist. I was given antibiotics and treated with drugs for prostate enlargement but continued to experience symptoms. Although skeptical of my presenting symptoms – an unremarkable prostate exam and PSA, the urologist eventually did biopsies that showed low-yield Gleason 6 prostate cancer. I consulted with 4 different doctors and all stated I was a candidate for active surveillance. After exploring all of my options with the last doctor, I decided to undergo a robotic prostatectomy. The pathology report upgraded my Gleason score of 6 to a 7 and most of the cancer was around my urethra near the bladder neck. So, I have two questions regarding active surveillance. First, how often is the amount of prostate cancer underestimated by initial biopsy results but still at an early enough stage for curative treatment? Secondly, how often is a biopsy Gleason 6 cancer upgraded after radical prostatectomy?

This is probably the most common question I get about active surveillance. If you have a routine transrectal ultrasound and biopsy, about 25-35% will be found to have either a higher Gleason or more extensive disease at diagnosis. Because of this fact, there is a major focus on improving the accuracy of the initial evaluation. There is a rather extensive urologic literature that focuses on how many biopsies are needed to accurately gauge the extent and aggressiveness of the cancer. In general, the more biopsies, the greater the accuracy all the way up to saturation biopsy protocols that can involve more than 50 biopsies.

Obviously, there is a market for less intrusive approaches. In response, there has been an effort to improve imaging of the prostate gland. Multiparametric MRI looks very impressive, but is still at an early stage. We have had a rather extensive experience referring patients to Dr. Bahn in Ventura California for color Doppler ultrasound. For years, we have referred Gleason 6 cases that look eligible for active surveillance to him for further evaluation. Interestingly, in about 30% of the cases, he finds disease too extensive or too aggressive for active surveillance.

There is yet another way to look at your question. How often does active surveillance result in patients progressing beyond organ-confined disease before patients are referred to surgery? Dr. Ballentine Carter at Johns Hopkins has looked at this. In their trial, this was an uncommon event. So, in skilled hands, cases like yours would be identified and referred to surgery in a timely fashion.

Finally, your question infers that your cancer was dangerous and caught in time by curative treatment. This is a common misconception among patients and even among practicing urologists. A portion of Gleason 3+4=7 cancers are just as indolent and nonthreatening as Gleason 6 and do well with active surveillance. So, it is still not clear that surgery benefited you. Conversely, there are also Gleason 3+4=7 cancers that are quite aggressive and have spread via the blood stream prior to surgery.

For this reason, prostatectomy is not a sure cure and there is a significant risk of recurrent disease. The PIVOT trial tried to quantify this by randomizing between watchful waiting and surgery. For Gleason 6 and PSA under 10, there was no survival advantage to surgery out to 12 years. For the higher Gleason grades, there was a survival advantage to surgery, but still far too many patients relapsed and died. So, I do not agree with your conclusion that your results truly establish that you benefited from surgery.

US TOO WANTS TO ANSWER YOUR QUESTIONS!

Dr. Myers would love to provide direct answers to questions posed by Us TOO members. Instead of printing questions answered in the *Prostate Forum*, we'd rather provide readers who subscribe to both publications with fresh content. Questions about imaging, active surveillance, and biochemical relapse would be particularly appreciated right now.

If you have questions, please send them to <Jackie@ustoo.org> or call the Helpline at 800-808-7866.

STATS DON'T LIE

(Continued from page 1)

Study Summary

In this article, Carter provides current statistics on the treatment of patients with low-risk disease and discusses definitions of "low-risk" disease and current guidance for pursuing close observation rather than immediate intervention.[1]

Can we define low-risk disease? Carter reviews two classification schemes from D'Amico and colleagues and Epstein and colleagues that have stood the test of time. However, there has been significant upgrading on surgical specimens, which has led to the recommendation for repeated biopsies in patients receiving close observation.

What do we know about patients with low-risk prostate cancer? Currently, patients with localized low-risk disease should be given the option of close observation. They should be informed that intervention with surgery or radiation reduces cancer-specific mortality by 50%, but that their cancer-specific mortality risk without treatment is less than 10%. These patients also need to be aware that the risk for cancer spread is low but does exist.

In the longest prospective study of 450 men followed with active surveillance for a median of 7 years, 10-year actuarial cancer-specific survival was 97% (and 17% of the patients were not low risk on entry).[2] Also, in a multi-institutional study, the 5-year probability of a patient remaining on active surveillance was 75%.[3]

In the future, identification of new molecular markers will give us a better definition of low-risk prostate cancer. At the present time, however, patients with low-risk disease should be informed about the pros and cons of close observation. Carter offers guidance for urologists in helping patients make an informed treatment choice.

References

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2. Klotz L, Zhang L, Lam A, et al. J Clin Oncol 28: 126-31, 2010
3. Eggener SE, Mueller A, Berglund RK, et al. J Urol 181: 1635-41, 2009

Edwin D. Vaughan, MD, for Medscape Urology Viewpoints 12 April 2012

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

"No, selenium cannot be considered safe for prostate cancer in really high-doses! Why hasn't this been objectively reported?"

Mark A. Moyad, MD, MPH
University of Michigan Medical Center, Department of Urology

Editors' 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: A lot of news sources reported in 2011 and continue to report in 2012 that selenium had absolutely no impact or might reduce risk of prostate cancer from the SELECT trial (largest randomized study in human history to determine if Vitamin E and/or Selenium can reduce the risk of prostate cancer) and other prostate cancer trials, but in reality there was an interesting non-significant higher risk of aggressive prostate tumors (Gleason 7+) found in each supplement group over the placebo in the SELECT trial and other lessons in other studies. Where was that reported???

Some folks have a tough time accepting the fact that too much of a good thing, including some dietary supplements are not a good thing! It is kind of like a hotdog and a beer at the baseball game (or too much sushi or too much exercise)…the first one tastes dang good and probably does no harm but eating and drinking 3-4 of these things in no time could ensure that you will be making a visit to the local restroom accepting a facedown position above the toilet seat (college flashback for Moyad)! When the results of the SELECT trial [1] came out and clearly showed an increased risk of prostate cancer with one type of vitamin E supplement in large doses there were many that stated that at least 200 micrograms of selenium per day was found to be safe and the combination of selenium and vitamin E were safe, but since I have no life and actually read all articles line by line in their entirety there was one finding that was not widely reported that should have been reported. Let me share with you Table 3 from that citation (on page 1552). Something amazing is found in men in this trial that were diagnosed with Gleason 7 or greater tumors (in other words Gleason 7, 8, 9 and 10 combined). In the vitamin E group alone there was a non-significant 16% greater risk of being diagnosed with a Gleason 7-10 cancer. In the selenium alone group there was a 21% increased risk that almost reached significance (p=0.11), and in the combination of vitamin E and selenium group there was a 23% HIGHER RISK that almost also reached significance (p=0.08)! Now, most of this was due to Gleason 7 cancers because there were few Gleason 8-10 cancers diagnosed in this trial (from table 4). And, selenium showed an increased risk of type 2 diabetes after 5.5 years but this risk decreased after stopping these supplements.

WOW! Some would say that the researchers did not test the right type of vitamin E and that a more natural form such as gamma-tocopherol or mixed vitamin E supplement should have been tested, but it is easy to be a Monday morning quarterback here. The fact that in all the supplement groups there was a non-significant increase risk of being diagnosed with aggressive prostate cancer (notably Gleason 7) is concerning and at least NEEDS TO BE SHARED!!

Interestingly, in another phase 3 US trial of selenium in men at high-risk for prostate cancer published last year there was a non-significant reduction in prostate cancer with selenium in the men that had the lowest levels of selenium to start the clinical trial! [2] Finally, a US trial in men with localized prostate cancer on active surveillance found a significantly higher PSA velocity in those that took 800 micrograms of selenium per day compared to placebo when they had already started the trial with higher levels of selenium in their blood! [3]

Let's face the facts…until someone proves to me that more is better…I will stick with less is more when it comes to prostate cancer. It seems that more is only better when you are getting little to none of a good thing in your diet and other pills. I don't mind a little selenium and vitamin E in my children's multivitamin but no thanks to megadoses for now!

Peace and Love, Mark A. Moyad.

References

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Want to learn more about local prostate cancer support group activities? Read the

CHAPTER NEWS!

at www.ustoo.org!

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

Author: *Winning The Battle Against Prostate Cancer, 2011*

Editors' 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 An important article by Salonen and co-workers addresses the issue of intermittent hormone therapy for men with advanced or metastatic prostate cancer. This is a well-done study with the authors recommending that intermittent hormone therapy should be the standard therapy offered to men who are appropriate candidates. That would mean their PSA declined below a defined level after hormone therapy was initiated. The advantages to patients are potentially improved quality of life and lower cost. One problem not addressed but pointed out in another randomized study of intermittent vs. continuous therapy was the following; men on intermittent therapy are more likely to die of prostate cancer but less likely to die of other causes. This point should be presented to every man who is considering intermittent therapy. The next question is whether more intense monitoring of overall health issues could further reduce the non-prostate cancer deaths in men on continuous therapy.

THE BOTTOM LINE: Intermittent hormone therapy appears to offer similar survival to some men with advanced or metastatic prostate cancer but it does so while allowing more men to die of prostate cancer but having a lower chance of dying of other causes.

a2p1c2 The article about Provenge is very important for a few reasons. First, although men have been told that the randomized study showed an improvement in survival of 4.1 months, many patients and doctors have been reluctant to take or recommend it because the benefit seems very small given the high cost. However, Gomella presented evidence that the true benefit of this treatment probably is actually much greater because many of the men in the control group actually were able to receive Provenge after their cancer progressed. This is called a crossover design. The downside to this approach is that it may lessen the apparent benefit. As for the article written by Huber and others raising questions about whether Provenge really works, her questions were addressed by the FDA and found to not be supported.

THE BOTTOM LINE: Provenge remains a reasonable option for asymptomatic or minimally symptomatic men with progressive metastatic disease who have a testosterone level below 50 ng/dL.

a3p1c3 The article adapted from Medscape by Dr. Vaughan talks about the growing recognition that many men are being over treated for their prostate cancer. Our understanding of which patients have little to gain from immediate therapy is definitely improving. In fact, an excellent article by Vickers has looked at the results from the Scandinavian trial comparing radical prostatectomy to watchful waiting and found that treating men over 70 with a Gleason 6 or 7 cancer, T1 cancer did not reduce their chance of dying from prostate cancer in 10 years. We can now be more specific than stated by Dr. Vaughan in the way men are counseled. The challenge is to really supply all the facts in an easy to understand manner. Telling men there is a 50% reduction in the death rate from prostate cancer is incomplete information. They also need to know that perhaps 5-6% will die of their disease without treatment compared to only 3% if they undergo surgery. Men will be unable to accept active surveillance if they continue to have inaccurate expectations of the risk from their cancer and the benefit from treatment.

THE BOTTOM LINE: Many more men could safely undergo active surveillance than are currently choosing it. The key is to inform them more accurately about the risk and benefit from treatment compared to observation

a4p2c2 Yet another article by Wernicke and co-workers addresses the treatment of men with intermediate risk prostate cancer using a combination of external radiation and permanent seed implantation. This study is important for several reasons, most importantly because it does NOT permit any valid conclusions about the best way to treat men with intermediate risk disease. This was a retrospective rather than a prospective randomized study, which means considerable selection bias may have occurred. One example is that the median size of the prostate was much smaller in the men getting Palladium. Other reasons are that the choice of isotope and the use of hormone therapy were solely at the discretion of the physician. Another point about hormones is that data from two randomized studies of intermediate risk group patients proved that hormone therapy + radiation improved overall survival compared to radiation alone. This study does not report survival but instead uses PSA, which is not a valid alternative for determining effectiveness and it provides no information about the side effects of either option. Finally, this study says nothing about whether combining brachytherapy with external radiation is as good, better, or inferior to radiation plus hormone therapy in terms of survival or quality of life.

THE BOTTOM LINE: At the current time, there is no way to determine if Iodine is a better isotope than Palladium or if the combination of external radiation plus brachytherapy is a good therapy for intermediate risk cancer in terms of its effect on long-term survival or quality of life as compared to other options.

a7p4c2 A very important article has been published about the activities that should be modified in people with cancer. Eat more fruits and vegetables, get a good amount of exercise weekly, avoid being overweight and do not take supplements are the key messages. These recommendations are based on the best studies available. Unfortunately, not enough doctors include these recommendations along with their cancer treatment advice. Many men may be surprised by the recommendation to not take supplements but the facts are that they have never been proven to help men with this disease, even though they do something to cancer cells in the laboratory. The facts are that some of them are now being recognized as harmful and men should be more cautious about what they take.

THE BOTTOM LINE: Men with prostate cancer should eat more fruits and vegetables, get regular exercise, avoid obesity and be very cautious about taking vitamins, herbs and supplements.

NUTRITION GUIDELINES

(Continued from page 4)

The new guidelines stress the importance of natural sources of vitamins and minerals as opposed to using dietary supplements. This practice has now "come under scrutiny," the authors note. "More recent data suggest that multivitamin supplements may actually increase the risk of mortality among healthy individuals, or at the very least, may not be helpful."

The guidelines also discuss evidence relating to specific cancer types, including breast, colorectal, endometrial, ovarian, lung, prostate, upper gastrointestinal, and head and neck cancers, and hematologic malignancies.

"Physicians and other healthcare providers have a unique opportunity to guide cancer patients toward optimal lifestyle choices, and thus can favorably influence the survivorship trajectory," the authors write. "The power of physician advice in facilitating preventive health behavior has been consistently demonstrated," they note.

OVERALL SURVIVAL WITH PROVENGE *(Continued from page 4)*

"The survival difference was dramatically different," Gomella said during his IPCC presentation. "If you exclude the frozen product, you actually get a much more dramatic and a much more robust response of about 10 to 12 months." In an interview, Gomella added, "From my viewpoint, the benefit of sipuleucel-T has been understated because many of the patients who received the frozen product who were on the control arm actually enjoyed a longer survival, decreasing the difference between the control arm and the treatment arm.

Gomella's analysis stands in sharp contrast to the contentions of Huber et al, who argue that previously unpublished trial data show worse OS in older versus younger patients in the placebo groups, and that the difference may stem from the study design.[2]

They contend that the placebo intervention itself may have adversely affected older patients in the placebo arm and therefore enhanced the sipuleucel-T survival advantage. "Because two-thirds of the cells harvested from placebo patients, but not from the sipuleucel-T arm, were frozen and not reinfused, a detrimental effect of this large repeated cell loss provides a potential alternative explanation for the survival 'benefit,'" the authors said.

In his IPCC presentation, Gomella said researchers are debating the impact of extracting immune cells, but that a study pending publication indicates the "number of immune cells you pull out of the body with leukapheresis is clinically insignificant."

Meanwhile, Dendreon Corporation based in Seattle, Washington, the company that developed Provenge, is continuing to investigate the vaccine for men with earlier-stage prostate cancer.

References

1. Gomella LG, Nabhan C, Whitmore JB, et al. Presented at the 2011 ASCO Annual Meeting, Chicago, IL, Abstract 4534.
2. Huber ML, Haynes L, Parker C, et al. J Natl Inst 104(4): 273-279, 2012.

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