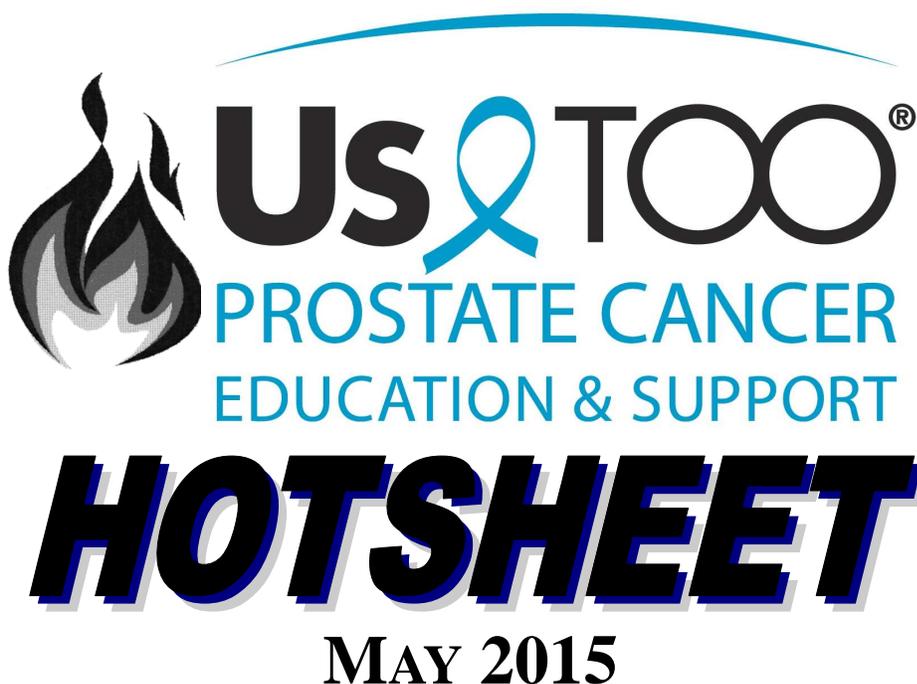


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NEW DATA REVIVE PROSTATE CANCER ACTIVE SURVEILLANCE DEBATE

Active surveillance (AS) for men with low-risk prostate cancer reduces over-treatment, but it could also mean that some men miss the opportunity for cure, according to the Göteborg randomized population-based prostate cancer screening trial. An investigator, Rebecca Arnsrud Godtman, MD, from the University of Gothenburg in Sweden presented this data at European Association of Urology (EAU) 30th Annual Congress.

"What we see now is that some men actually die from prostate cancer while on AS," said Dr Godtman. "It is not clear whether men who are not in the lowest-risk group, and who have many years of life-expectancy remaining, are suitable candidates for this strategy. Men should be informed about this before entering an AS program," she explained. It can be hard to detect disease progression, and it might be found "too late, when they are beyond the point of cure."

All men were 50 to 64 years of age when they enrolled in the trial, and 1,050 prostate cancers were detected as a result of the screening. Of these, 457 men (mean age, 69.5 years) chose AS. "The most common reason to pursue AS was a presumed low-risk prostate cancer, but it could also have been due to patient preference or comorbidities," Dr. Godtman explained.

(Continued on page 4)

ABIRATERONE BEFORE CHEMO IMPROVES SURVIVAL: LABEL UPDATE

The US Food and Drug Administration (FDA) has approved a label update for abiraterone acetate (Zytiga®, Janssen Pharmaceuticals, Inc.), which now states that the drug significantly improves survival as compared with placebo when given before chemotherapy to men with metastatic castration-resistant prostate cancer (mCRPC). Zytiga had already been approved by the FDA for this indication, but the new label specifically mentions the survival benefit.

The label update is based on the final analysis of that study, known as COU-AA-302, which has now been published online 15 January 2015 in *Lancet Oncology*. The focus of the current article was an update of overall survival (OS) and the secondary endpoint of time to opiate use for cancer-related pain.

Zytiga received FDA approval in April 2011 as a second-line treatment following docetaxel chemotherapy for men with MCRPC. In December 2012, that indication was expanded to include use in the first-line setting on the basis of an interim analysis of a randomized phase 3 trial that showed that progression-free survival (PFS) was significantly longer in the Zytiga group than in the placebo group.

At the time of the interim analysis, median OS had not yet been reached in the

(Continued on page 5)

RADIATION AFTER PROSTATECTOMY: DEBATE OVER TIMING

Among men with newly diagnosed prostate cancer who are offered radical prostatectomy (RP) with curative intent, around 60% of patients have high-risk features, which are associated with cancer recurrence. In these patients, radiation therapy (RT) after surgery is expected to improve cure rates.

In clinical practice, there is uncertainty about the timing of RT. Should it be given soon after RP (adjuvant RT), or only after biochemical recurrence (BCR), when levels of PSA rise? Two new studies could add to the debate on whether RT should be provided after RP or after BCR as salvage RT, but overall, both studies provide confidence to those who offer adjuvant RT. The two longitudinal studies are based on analyses from Italian and Surveillance, Epidemiology, and End Results (SEER)–Medicare databases of cohorts of men who received RP and included men who received postsurgical RT.

The Italian study was published in the March 15 issue of the *International Journal of Radiation Oncology, Biology, Physics* (Vol 91, p 752–759, 2015). Timothy J. Showalter, MD, MPH, radiation oncologist and colleagues from the University of Virginia School of Medicine in Charlottesville, VA, accessed data from the Regione Emilia-Romagna

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2720 S. RIVER RD., STE. 112, DES PLAINES, IL 60018
PHONE: (630) 795-1002 / FAX: (630) 795-1602

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ACTIVITY OF ENZALUTAMIDE IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IS AFFECTED BY PRIOR TREATMENT WITH ABIRATERONE AND/OR DOCETAXEL

Cheng HH, Gulati R, Azad A, et al

Prostate Cancer Prostatic Dis
20 January 2015; Epub

Background: Enzalutamide and abiraterone are new androgen-axis disrupting treatments for metastatic castration-resistant prostate cancer (mCRPC). We examined the response and outcomes of enzalutamide-treated mCRPC patients in the real-world context of prior treatments of abiraterone and/or docetaxel.

Methods: We conducted a seven-institution retrospective study of mCRPC patients treated with enzalutamide between January 2009 and February 2014. We compared the baseline characteristics, PSA declines, PSA progression-free survival (PSA-PFS), duration on enzalutamide and overall survival (OS) across subgroups defined by prior abiraterone and/or docetaxel.

Results: Of 310 patients who received enzalutamide, 36 (12%) received neither prior abiraterone nor prior docetaxel, 79 (25%) received prior abiraterone, 30 (10%) received prior docetaxel and 165 (53%) received both prior abiraterone and prior docetaxel. Within these groups, respectively, $\geq 30\%$ PSA decline was achieved among 67, 28, 43 and 24% of patients; PSA-PFS was 5.5 (95% CI 4.2-9.1), 4.0 (3.2-4.8), 4.1 (2.9-5.4) and 2.8 (2.5-3.2) months; median duration of enzalutamide was 9.1 (7.3-not reached), 4.7 (3.7-7.7), 5.4 (3.8-8.4) and 3.9 (3.0-4.6) months. Median OS was reached only for the patients who received both prior abiraterone and docetaxel and was 12.2 months (95% CI 10.7-16.5). Twelve-month OS was 78% (59-100%), 64% (45-90%), 77% (61-97%) and 51% (41-62%). Of 70 patients who failed to achieve any PSA decline on prior abiraterone, 19 (27%) achieved $\geq 30\%$ PSA decline with subsequent enzalutamide.

Conclusions: The activity of enzalutamide is blunted after abiraterone, after docetaxel, and still more after both, suggesting subsets of overlapping and distinct mechanisms of resistance.

THE DIFFUSION OF DOCETAXEL IN PATIENTS WITH METASTATIC PROSTATE CANCER

Unger JM, Hershman DL, Martin D, et al

J Natl Cancer Inst 2015; 107; Epub

Background: Diffusion of new cancer treatments can be both inefficient and incomplete. The uptake of new treatments over time (diffusion) has not been well studied. We analyzed the diffusion of docetaxel in metastatic prostate cancer.

Methods: We identified men with castrate-resistant prostate cancer (CRPC) diagnosed from 1995 to 2007 using the Surveillance, Epidemiology, and End Results Program (SEER)-Medicare database. Medicare claims through 2008 were analyzed. We assessed cumulative incidence of docetaxel by socioeconomic, demographic, and comorbidity variables, and compared diffusion patterns to landmark events including release of phase III results and FDA approval dates. We compared docetaxel diffusion patterns in prostate cancer to those in metastatic breast, lung, ovarian, and gastric cancers. To model docetaxel use over time, we used the classic "mixed influence" deterministic diffusion model. All statistical tests were two-sided.

Results: We identified 6561 metastatic CRPC patients; 1,350 subsequently received chemotherapy. Among patients who received chemotherapy, docetaxel use was 95% by 2008. Docetaxel uptake was statistically significantly slower ($P < 0.01$) for patients older than 65 years, blacks, patients in lower income areas, and those who experienced poverty. Eighty percent of docetaxel diffusion occurred prior to the May, 2004 release of phase III results showing superiority of docetaxel over standard-of-care. The maximum increase in the rate of use of docetaxel occurred nearly simultaneously for prostate cancer as for all other cancers combined (in 2000).

Conclusion: Efforts to increase the diffusion of treatments with proven survival benefits among disadvantaged populations could lead to cancer population survival gains. Docetaxel diffusion mostly preceded phase III evidence for its efficacy in CRPC, and appeared to be a cancer-wide – rather than a disease-specific – phenomenon. Diffusion prior to definitive evidence indicates the prevalence of off-label chemotherapy use.

**DOC MOYAD’S WHAT WORKS & WHAT IS WORTHLESS COLUMN,
ALSO KNOWN AS “NO BOGUS SCIENCE” COLUMN –**

“Start low, go slow and you will always save side effects and dough?!”

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

Editor’s Note: Us TOO invites 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 are not necessarily those of Us TOO International.

Bottom Line:

When starting any pill from a multivitamin to a statin, aspirin, or even metformin try to start either with the lowest dose or even try a children’s dose to see how well you might tolerate the drug or supplement and always take pills with or around meals/food (unless stated otherwise, of course).¹

Here are some things I hear at support group lectures. “Dr. Moyad, you are so beautiful that you should be a full-time male international model.” Or, “Dr. Moyad, you are the most lean and muscular, handsome and smartest human being I have ever met!”

Okay, well I might have embellished those previous two statements, so let me really tell you what I often hear at lectures. “Dr. Moyad, I took 1,500 mg of metformin and got diarrhea; Dr. Moyad, I took 40 mg of a cholesterol-lowering drug or statin and my muscles and joints ache; Dr. Moyad, I took a full-strength aspirin and my stomach hurt; and Dr. Moyad, I took a multivitamin packet and my skin started itching.”

What all these situations have in common is the fact that these individuals were perfect for the Moyad saying (already patented, so if you use it you owe me one non-light beer) when it comes to any pill, “start low, go slow and you will always save side effects and dough!” In other words, when starting most pills (except FDA prostate cancer medications) try and take the lowest dose possible for at least two weeks and usually with food (unless it states otherwise). In that way, you can see how well you tolerate the product and get your body acclimated to the pill. This will lower your chances of side effects, save money, allow you more time to add in more lifestyle changes and help you determine, with the doctor you trust most, if you even need the dosage recommended.

For example, let’s look at metformin. If you start with 500 mg per day for two

weeks with food, and then increase the dose to 500 mg per day, the chances of experiencing diarrhea or a loose stool are reduced. In addition, if you exercise and eat better when you start this pill perhaps your blood sugar will be reduced enough so that you never need much higher doses of the drug such as 1,500 or 1,700 mg per day. The same holds true for a statin where you could start with just five or 10 mg per day for several weeks and exercise and eat better and perhaps you may actually never need a higher dose and the side effects associated with it.

Many of us assume that just because a dosage is recommended that this is the exact dosage needed when you start taking the pill. I say, “Not really folks,” of course, just as a suggestion. As another example, look at aspirin. For decades, experts thought the full-strength dose was best but now we know that for most folks a baby aspirin provides many of the same benefits as a full-strength aspirin with reduced toxicity. There are more examples I can mention. For multivitamins, many adult patients will do fine taking a Centrum Kids or another children’s multivitamin compared to a full-strength pill. For side effects from allergy pills, many patients will do fine with a children’s product or dose, and the beat goes on. Many folks I speak with tell me that this is even the case with many pain medications. My kid was told he HAD TO HAVE Vicodin® (that is insane by the way) for wisdom teeth extractions. I gave him Aleve® instead and it worked very well and he never knew the difference. An additional benefit was it potentially reduced the chances of him becoming addicted to pain medications. In fact, as of now I am adding to my iconic saying “Start low, go slow, and you will save side effects and dough” to include “and send that extra dough to Moyad for his beer fund.” Okay! Not as catchy I know!

Reference:

1. Moyad MA. The Supplement Handbook (Rodale Publishing), 2015.

**ACTIVE SURVEILLANCE IN
INTERMEDIATE-RISK PROSTATE
CANCER CARRIES A FOURFOLD
HIGHER 15-YEAR MORTALITY
RISK**

An analysis of data on roughly 945 patients with prostate cancer managed with active surveillance (AS) has shown differences in outcomes depending on whether the cancer was low- or intermediate-risk at diagnosis. Compared to patients with low-risk disease, those with intermediate-risk cancer (PSA >10 ng/mL or Gleason score 7 or clinical stage T2b/2c) had a nearly fourfold higher chance of dying from prostate cancer within 15 years. This conclusion was announced the Genitourinary Cancers Symposium, held from February 26 to 28, 2015, in Orlando, FL.

Andrew Loblaw, MD, of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, explained that AS is a globally recognized standard approach for patients with low-risk prostate cancer and select intermediate-risk patients with prostate cancer. Cancer Care Ontario recently released guidelines recommending AS for the preferred approach for low-risk patients. Men on AS undergo physical examinations, digital rectal examinations, PSA measurements, and repeat tumor biopsies. He said that this was the first study to examine long-term outcomes of men with low- vs. intermediate-risk prostate cancer managed on AS.

The researchers analyzed prospectively collected data on 945 men (237 with intermediate-, 708 with low-risk cancer) who were on AS between 1995 and 2013. Overall survival (AS) and cause-specific survival (CSS) for intermediate- and low-risk patients was analyzed as well as metastasis-free survival and treatment-free survival for intermediate-risk patients. Men whose disease worsened during AS were offered treatment (radiation or surgery). In the intermediate-risk group, 86 patients (36.3%) received treatment.

A total of 237 (23.9%) men had intermediate-risk disease, with a median follow-up of 6.9 years. A total of 708 patients had low-risk cancer, with a median follow-up of 6.4 years. A total of

(Continued on page 8)

NADIR TESTOSTERONE WITHIN FIRST YEAR OF ANDROGEN-DEPRIVATION THERAPY (ADT) PREDICTS FOR TIME TO CASTRATION-RESISTANT PROGRESSION: A SECONDARY ANALYSIS OF THE PR-7 TRIAL OF INTERMITTENT VERSUS CONTINUOUS ADT

Klotz L, O'Callaghan C, Ding K, et al
J Clin Oncol 2 March 2015; Epub

Purpose: Three small retrospective studies have suggested that patients undergoing continuous androgen deprivation (CAD) have superior survival and time to progression if lower castrate levels of testosterone (<0.7 nmol/L) are achieved. Evidence from prospective large studies has been lacking.

Patients and Methods: The PR-7 study randomly assigned patients experiencing biochemical failure after radiation therapy or surgery plus radiation therapy to CAD or intermittent androgen deprivation. The relationship between testosterone levels in the first year and cause-specific survival (CSS) and time to androgen-independent progression in men in the CAD arm was evaluated using Cox regression.

Results: There was a significant difference in CSS ($P=0.015$) and time to hormone resistance ($P=0.02$) among those who had first-year minimum nadir testosterone <0.7, 0.7 to ≤ 1.7 , and >1.7 nmol/L. Patients with first-year nadir testosterone consistently >0.7 nmol/L had significantly higher risks of dying as a result of disease (0.7 to 1.7 nmol/L: hazard ratio [HR], 2.08; 95% CI, 1.28 to 3.38; >1.7 nmol/L: HR, 2.93; 95% CI, 0.70 to 12.30) and developing hormone resistance (0.7 to 1.7 nmol/L: HR, 1.62; 95% CI, 1.20 to 2.18; ≥ 1.7 nmol/L: HR, 1.90; 95% CI, 0.77 to 4.70). Maximum testosterone ≥ 1.7 nmol/L predicted for a higher risk of dying as a result of disease ($P=0.02$).

Conclusion: Low nadir serum testosterone (i.e., <0.7 nmol/L) within the first year of androgen-deprivation therapy correlates with improved CSS and duration of response to androgen deprivation in men being treated for biochemical failure undergoing CAD.

NEW DATA REVIVE ACTIVE SURVEILLANCE DEBATE

(Continued from page 1)

In the AS group, the disease was classified as very low risk in 52% of the men, as low risk in 27%, as intermediate risk in 21%, and as high risk in 1%. Very low risk was defined by Epstein criteria as a Gleason score of ≤ 6 , involvement of less than one-third of cores, and an extent of core involvement of less than 50%. Low risk was defined as T1 disease, a Gleason score ≤ 6 , and a PSA level <10 ng/mL. Intermediate risk was defined as T1 to T2 disease, a Gleason score ≤ 7 , and a PSA level below <20 ng/mL. High risk was defined as T1 to T4 disease, a Gleason score ≥ 8 , and/or a PSA level >100 ng/mL.

AS involved PSA testing every three to six months, and rebiopsy every two to three years in the case of stable disease, or earlier if there were signs of disease progression. Over a median follow-up of eight years, 197 of the men discontinued AS. About 65% of these men went on to radical prostatectomy, 20% to radiation therapy, and 14% to hormonal treatment, Dr. Godtman reported.

"This resulted in a treatment-free survival rate of 63% at five years, 47% at 10 years, and 35% at 15 years," she said. For the 51 men whose disease progressed during AS, six died of prostate cancer, 20 had a PSA relapse, and 25 started hormone therapy. Therefore, the failure-free survival rate was 87% at 10 years and 75% at 15 years. In the Toronto cohort, which had been the longest

AS follow-up, cancer-specific mortality was 3% at 10 to 15 years.

"But caution is needed when comparing mortality data from the Göteborg study and more current surveillance programs," said Matt Cooperberg, MD, from the University of California at San Francisco. "These six patients who died were diagnosed in the 1990s in the context of a screening trial," he told Medscape Medical News. "It was not an AS protocol like we have today. At the time of progression, they already had incurable disease, and only one of the six was even offered a chance at curative therapy."

"The Göteborg study did not have a strict AS protocol. In addition, it is likely that some patients did not adhere to recommended PSA and biopsy follow-ups, in contrast to men in the Toronto cohort," he explained. "The fact is that the number of men who die because they choose AS is far, far lower than the numbers who are harmed by the side effects of overtreatment," Dr. Cooperberg stressed.

There were men who died on AS in the Toronto cohort. However, "the number is actually not that different from the proportion of men with what looked like low-risk cancer who were treated with surgery or radiation therapy and who died with similar follow-up."

Presented at EAU 30th Annual Congress, abstract 1034

Medscape Medical News, 1 April 2015

INFECTION ON THE RISE AFTER TRANSRECTAL PROSTATE BIOPSY

Infection rates after transrectal prostate biopsy are on the rise, and are "considerably higher" than they were a decade ago, a worldwide prevalence study suggests. The research, conducted from 2010 and 2013 as a side study of the Global Prevalence of Infections in Urology study, involved 1,214 patients from 136 countries. Patients biopsied during a two-week window each year were eligible for the study.

"We initiated this study in 2010 because of more and more evidence that infections after transrectal biopsy were a problem," said study investigator Florian Wagenlehner, MD, from the Justus-Liebig University in Giessen, Germany. "Among the prostate biopsies performed

around the world – and approximately one million are performed in Europe alone each year – there is a 'significant level' of infectious complications," he said here at the European Association of Urology (EAU) 30th Annual Congress.

Outcome data two weeks after biopsy were available for 876 men. Of this cohort, 97% had undergone transrectal biopsy and 98% had received prophylactic antibiotics (82% with fluoroquinolone-based agents). Of these men, 50% developed symptomatic urinary tract infections, 3% developed febrile urinary tract infections, and 4% were hospitalized for these infections. One man died

(Continued on page 5)

ABIRATERONE BEFORE CHEMOTHERAPY IMPROVES SURVIVAL*(Continued from Page 1)*

Zytiga group; it was 27.2 months in the placebo group. The mortality rate was lower in the Zytiga group, however, than in the placebo group (27% vs. 34%), with a 25% decrease in the risk for death (hazard ratio [HR], 0.75; $P=0.01$), “indicating a strong trend toward improved survival,” the study authors said at that time.

Now in the final analysis of the double-blind, placebo-controlled COU-AA-302 study, Zytiga plus prednisone significantly prolonged median OS compared with placebo plus prednisone in this population of chemotherapy-naïve men with mCRPC. After a median follow-up period of 49.2 months, men in the Zytiga group had a median overall survival of 34.7 months, as compared with 30.3 months in the placebo plus prednisone arm (HR, 0.81; 95% confidence interval [CI], 0.70–0.93; $P=0.0033$).

The study included 1,088 asymptomatic or mildly symptomatic men with chemotherapy-naïve prostate cancer who were randomly assigned in a 1:1 ratio to receive either Zytiga (1,000 mg once daily) plus prednisone (5 mg twice daily) or placebo plus prednisone. At the time of the final analysis, 42 men (8%) in the Zytiga group were still receiving treatment. A total of 238 (44%) patients in the placebo group subsequently went on to receive Zytiga, either as a crossover per protocol (93 men) or as subsequent therapy (145 patients).

Overall, 365 (67%) men in the Zytiga group and 435 (80%) in the placebo group did receive subsequent treatment with one or more approved agents. The risk for death was significantly lower in the Zytiga group than in the placebo group (HR, 0.81; 95% CI, 0.70–0.93; $P=0.0033$). The results on final analysis showed that 354 of 546 men (65%) in the Zytiga group had died, compared with 387 of 542 (71%) in the placebo group.

When looking at the secondary endpoint, men in the Zytiga group had a longer interval to needing opiates for pain. The median time to opiate use for prostate cancer-related pain was 33.4 months in the Zytiga group vs. 23.4 months in the placebo group.

The authors observed that there were no notable changes in the safety profile of Zytiga since the previous interim analyses were reported. The most common grade 3-4 adverse events of special interest were cardiac disorders (41 [8%] patients in the Zytiga group vs. 20 [4%] in the placebo group), increased alanine aminotransferase levels (32 [6%] vs. four [$<1\%$]), and hypertension (25 [5%] vs. 17 [3%]).

In an accompanying editorial, Ravi Madan, MD, and William L Dahut, MD, both of the National Cancer Institute, note that new treatment strategies are changing the paradigm of MCRPC. They point out that during the past five years, there have been seven phase 3 trials, including this one, that have significantly extended survival in this patient population. The studies have used five different therapeutic modalities, including anti-androgens, chemotherapy, immunotherapy, and radiopharmaceuticals.

“This is a remarkable series of advancements that have substantially altered how metastatic castration resistant prostate cancer is treated,” they write. But now is the time to aim higher.

“Although noteworthy delays of disease progression are valuable, an increase in the proportion of patients achieving cure is the ultimate goal,” Dr. Madan and Dr. Dahut write.

They speculate as to whether Zytiga or any other emergent therapy can enhance the curative intent of radiation or surgery or whether it is possible to minimize mechanisms of resistance if tumor volume and heterogeneity are low at diagnosis. “Fueled by the remarkable revolution in therapies for mCRPC, a new generation of clinical trials should bring these therapeutic advances to bear on the tumour when it is localised, with hopes of downstaging the disease before radiation or surgery,” the editorialists suggest.

“We should no longer settle for shifting Kaplan-Meier curves in metastatic prostate cancer; instead, we should focus on finding ways to shift paradigms by using these therapies to enhance cure rates at diagnosis,” they conclude.

Medscape Medical News, 1 April 2015

BIOPSY INFECTIONS*(Continued from page 4)*

as a result. “These rates are significantly higher than results published in the 1990s, showing febrile urinary tract infections around 1%, so there’s definitely a higher rate now,” Dr. Wagenlehner said.

“This infection prevalence information is very valuable for clinicians,” said Michael Liss, MD, from the University of Texas Health Science Center in San Antonio. “I use this information in counseling patients,” said Dr. Liss “If their risk of infection or hospitalization is higher than the chances of high-grade prostate cancer, I would recommend against prostate biopsy.”

Risk factors for infection – such as pre-operative bacteriuria, bowel preparation, antibiotic prophylaxis for more than one day – were not significantly different between patients who developed infection after biopsy and those who did not. “Our study did not find any risk factors, but we know from other studies that a major risk factor is fluoroquinolone resistance,” Dr. Wagenlehner said.

Dr. Liss pointed out that in this study, the researchers “could not control for the antibiotics given by the physicians.

Therefore, the physicians most likely selected the men at highest risk for infection and gave them alternative or additional antibiotics to prevent infection.”

“The idea of using antibiotics to try to avert fluoroquinolone resistance is nice,” said Karan Wahda, MD, from the University of Cambridge in the UK.

“Unfortunately, we’re going to run out of antibiotics soon and, despite our best efforts, we’re really not going to have anything in terms of prophylaxis,” he stated. “Transperineal prostate biopsy provides an alternative because it allows us to avoid the fecal route,” he added.

However, despite evidence that transperineal biopsies pose significantly less infection risk than the transrectal approach, this worldwide study shows that 97% of clinicians still use the transrectal route. “For the general practitioner urologist, the transperineal biopsy is not the first choice,” Dr. Wahda explained, “because the procedure requires that the patient be under general anesthesia.”

Medscape Medical News, 27 March 2015

RADIATION AFTER PROSTATECTOMY: DEBATE OVER TIMING (Continued from page 1)

Italian Longitudinal Health Care Utilization Database. They identified 9,876 men who underwent RP for prostate cancer from 2003 to 2009. Of the men in this cohort, 7,700 were treated with RP alone and 2,176 were treated with RT after RP.

As expected, RT after RP led to significantly higher rates compared to RP alone for gastrointestinal [GI] (1.55 vs. 0.99 events/100 person-years), urinary incontinence [UI] (2.34 vs. 1.24 events/100 person-years), and genitourinary [GU] (0.77 vs. 0.64 events/100 person-years) adverse events. In a statistical analysis, the timing of when men received RT was not associated with any increased risk for these events.

The second study was published online February 23 in PLoS ONE (Vol 10, p e0118430, 2015). Dr. Showalter and colleagues identified 523,153 men in the SEER–Medicare linked database who were diagnosed with prostate cancer from 1992 to 2007. From this cohort, 6,137 men were eligible for analysis – 4,509 treated with RP alone, 894 treated with adjuvant RT after RP, and 734 treated with salvage RT at least 12 months after RP.

As expected, adjuvant RT (13.87 events/100 person-years) and salvage RT (17.06 events/100 person-years) were associated with higher procedure-defined GI event rates than RP alone (13.87 events/100 patient-years). A similar trend

was seen for diagnoses-defined events. The event rate was higher for salvage RT than for adjuvant RT.

Procedure-defined GU event rates for UI were also lower for RP (5.88 events/100 person-years) than for adjuvant RT (6.58 events/100 person-years) or salvage RT (6.74 events/100 person-years). In both studies, erectile dysfunction rates were similar for adjuvant and salvage RT, and were similar to rates in men undergoing only RP.

“These are both well-conducted studies,” stated Anthony V. D’Amico, MD, PhD, professor in the Department of Radiation Oncology and chief of genitourinary radiation oncology at the Dana-Farber Cancer Center and the Brigham and Women’s Hospital. “The seemingly different conclusions from both studies arise from the fact that they were non-randomized studies, so all patient confounders could not be adjusted for. Each study can only generate a hypothesis that needs to be prospectively assessed in a randomized trial,” he explained.

Stacy Loeb, MD, MSc, assistant professor of urology and population health at New York University in New York, NY, was also approached for comment.

“Both studies show clearly that any RT after RP increases the risk of GU and GI toxicity. They did not find a statistically significant difference in the risk of complications based on whether RT was given earlier or later after surgery,” she

commented. “However, this does not mean that every man should be given adjuvant therapy.”

Dr. Loeb indicated that both studies had limitations. “The authors cannot actually determine whether the RT was given in an adjuvant or salvage scenario. They only know the date that it was received but not the actual clinical context,” she told Medscape Medical News. “In addition, we do not have any data on the extent to which patients’ quality of life was affected,” she said.

In an institution press release, Dr. Showalter said that “a lot of clinicians believe that if you wait six, 12 or 18 months, that each additional step gets you some benefit in terms of toxicity. That didn’t make sense to me from a medical perspective, because I can’t think of any other surgery where we think recovery requires a year or more. We often, for other cancers, deliver postoperative RT very soon,” Dr. Showalter said.

Dr. Zelefsky noted that “not all patients with risk factors for BCR ultimately develop a recurrence. That is why it might be prudent to wait until the development of early BCR. This will spare others unnecessary RT,” he added. Dr. Loeb agreed, stating “I believe in an early salvage approach for the majority of patients, and these studies will not change my practice.”

Medscape Medical News, 31 March 2015



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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 are not necessarily those of Us TOO International.

a1p1c1 & a9p6c1 When is the best time to give radiation therapy (RT) after radical prostatectomy (RP)? One randomized study found that overall survival (OS) is improved with early adjuvant RT but only one out of nine men benefited in 10 years. Delayed RT may have a smaller benefit, but the advantage is more than half the men can avoid RT. The studies cited in this *HotSheet* show that both early and late RT increases gastrointestinal (GI) and genitourinary (GU) toxicity. The question is whether delayed RT has a similar OS as immediate RT while sparing unnecessary treatment to many men.

The Bottom Line: Studies cited here suggest that delaying RT does not reduce toxicity so the ultimate decision will be based on the relative risk vs. the relative benefit. Results from the randomized studies are anxiously awaited.

a4p2c1 Is there an optimal sequence for the drugs available in men with CRPC? Studies are in progress to answer that important question. For now, uncontrolled studies are looking at the response of one drug in men who have received one or more of the other options. The study by Cheng et al looked at enzalutamide response in men who received abiraterone, docetaxel, both, or neither and found that the best result occurred in men who had never received either of the other two drugs. However, an important limitation of the study is that the authors did not look at OS starting from the initiation of any one of the drugs. To avoid a misleading conclusion they should have calculated the total time on advanced drug therapy. That means comparing OS of men receiving only enzalutamide to the OS of men from the time they began abiraterone and/or docetaxel followed by enzalutamide. In other words, it may not matter which drug came first, second, or third; total OS might be quite similar.

The Bottom Line: Although this study suggests a better response to enzalutamide in men who had not received either abiraterone or docetaxel, the finding needs more confirmation before it is used to make treatment decisions.

a7p3c3 Is active surveillance (AS) safe for men with intermediate-risk prostate cancer? A study from a Canadian group suggests that the risk of dying is significantly higher in men with intermediate-risk disease compared to those with low-risk disease. With a median follow-up of more than six years, 11.5% of men with intermediate-risk disease died from prostate cancer at 15 years compared to only 3.7% of those with low-risk disease. OS in the intermediate-risk group was 50% compared to 69% in the low-risk group. Although the risk of dying is clearly higher for the intermediate-risk group, there is another way of looking at these results. By 15 years, approximately 11/100 men (11%) with intermediate-risk disease died of their disease while 39/100 (39%) died of other causes. In other words, men were about almost four times more likely to die of other causes if they selected AS. Then, is AS a reasonable option for intermediate-risk disease? With careful selection, the answer still is yes, especially for men with life expectancy less than 15 years. Perhaps genomic testing can help this selection. More data are still needed to understand which men with intermediate-risk disease can safely select AS.

The Bottom Line: AS for men with intermediate-risk prostate cancer is not as safe as it is for men with low-risk disease but still can be considered based on a man's health and life expectancy.

a8p4c1 How important is reaching a very low testosterone (T) level during ADT? The study by Klotz and co-workers suggests that reaching a T level below 20 ng/dL during the first year of therapy is predictive of improved survival. Other uncontrolled studies also have suggested that a low T level during ADT is advantageous. Unfortunately, not all laboratories are capable of measuring T concentrations when they are below 50 ng/dL, although patients can request that the test be performed by a reference laboratory with a more sensitive analytical method. Ideally, a prospective study would be done to truly prove that lower T is really better. Until then, data continue to accumulate in

support of it. The best advice for men going on ADT is to monitor their T level periodically and if it remains higher than 20 ng/mL consider asking their doctor to changing to a different drug treatment.

The Bottom Line: More data are accumulating that men on ADT respond better if their serum T level on treatment is below 20 ng/mL.

a9p4c2 The study by Wagenlehner and co-workers raises new concerns about infections associated with transrectal prostate biopsy. In a large cohort study, they found that 50% of men developed a urinary tract infection. It is unclear what approaches were used for prophylaxis but there are growing concerns that resistance to fluoroquinolones are on the rise. The exact reason for this is unclear but it could be growing bacterial resistance to this class of drugs. Another possibility is that the way it is being used is not optimal. Oral antibiotics need at least 20 minutes to achieve good blood levels and it is unclear how long doctors wait before doing the biopsy. Regardless, transrectal biopsy does appear to have more risk than in the past.

The Bottom Line: Men should be counseled about the rising risk of infection following a transrectal prostate biopsy.

a10p8c2 Does medical or surgical castration increase the risk of a cardiovascular event? That question has been addressed many times in previous issues of the *HotSheet*. Randomized studies have not found an increase but uncontrolled studies such as the one by O'Farrell et al have found an increased risk. Current recommendations do not exclude ADT therapy for appropriate patients but anyone with any cardiac symptoms should be carefully evaluated before initiating ADT. Also, men should be monitored during ADT because it can increase cholesterol and triglycerides, lower hematocrit, and causes weight gain, which may increase a man's risk of a cardiovascular event.

The Bottom Line: Conflicting data continue about the cardiovascular risk of ADT so men should be aware of the need for careful medical evaluation.

AS & INTERMEDIATE RISK PCA

(Continued from page 3)

61.2% of the intermediate-risk cohort was older than 70 years of age.

The 10-year and 15-year OS rates were 68.4% and 50.3% for intermediate-risk patients compared to 83.6% and 68.8% for low-risk patients. The lower survival rate for intermediate-risk patients offered AS suggests that these patients had lower life expectancy. Patients with intermediate-risk disease had a 3.75 times higher chance of dying of prostate cancer compared to patients with low-risk disease (11.5% vs 3.7% at 15 years, respectively).

Dr. Loblaw concluded, “For low-risk patients with prostate cancer managed with AS, the risk of dying of prostate cancer is low, validating this approach for this group of patients. More research, however, is needed to better characterize intermediate-risk patients who can safely be monitored in a surveillance program.” He urges extreme caution in using AS for intermediate-risk patients.

Practice Update, 23 February 2015

GONADOTROPIN RELEASING HORMONE AGONIST TREATMENT AND ORCHIECTOMY LINKED TO INCREASED RISK OF CARDIOVASCULAR DISEASE IN MEN WITH PROSTATE CANCER

In a study of Swedish men with prostate cancer reported online in the *Journal of Clinical Oncology* (*J Clin Oncol* 2 March 2015, Epub), O’Farrell et al found that use of gonadotropin releasing hormone (GnRH) agonists and orchiectomy were associated with a significantly increased risk of incident cardiovascular disease. In patients with prior cardiovascular disease, risk for a cardiovascular event within 6 months of starting androgen deprivation therapy (ADT) was significantly increased with GnRH agonist use, antiandrogen use, and orchiectomy.

The study involved data from Swedish national health-care registers on 41,362 men with prostate cancer on ADT and an age matched cohort of 187,785 men without prostate cancer. From 2006 to 2012, 10,656 men were on antiandrogens, 26,959 were on GnRH agonists, and 3,747 underwent orchiectomy.

Compared with the prostate cancer-free cohort, incident cardiovascular disease risk was significantly increased in men using GnRH agonists (hazard ratio [HR]

1.21, 95% confidence interval [CI], 1.18–1.25) and men who had undergone orchiectomy (HR 1.16, 95% CI, 1.08–1.25), whereas men using antiandrogens had a decreased risk (HR 0.87, 95% CI, 0.82–0.91). Cardiovascular disease risk was highest during the first 6 months of ADT in men with at least two cardiovascular events before therapy; HRs were 1.91 (95% CI, 1.66–2.20) in those on GnRH agonists, 1.60 (95% CI, 1.24–2.06) in those on antiandrogens, and 1.79 (95% CI, 1.16–2.76) in those with orchiectomy vs. the comparison cohort.

The investigators concluded: “Our results support that there should be a solid indication for [ADT] in men with [prostate cancer] so that benefit outweighs potential harm; this is of particular importance among men with a recent history of [cardiovascular disease].”

Sean O’Farrell, BSc, MRes, of King’s College London, is the corresponding author of the *Journal of Clinical Oncology* article.

The ASCO Post, 1 April 2015

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