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HOTSHEET

DECEMBER 2014

SEQUENCING RADIUM-223 AND DOCETAXEL IN PROSTATE CANCER

The novel radiopharmaceutical for prostate cancer, radium Ra 223 dichloride (Xofigo®), is equally effective whether or not the patient has previously received chemotherapy with docetaxel, a new analysis concludes. The product was approved last year for the treatment of metastatic castration-resistant prostate cancer (mCRPC) on the basis of results from the ALSYMCA study.

Now, the ALSYMCA investigators report a prespecified analysis that shows that radium-223 is effective in these patients, regardless of previous docetaxel (DOC) use. The report was published online October 17 in the *Lancet Oncology*.

In an accompanying comment, Robert B. Den, MD, and W. Kevin Kelly, DO, from the departments of radiation and medical oncology, respectively, at Thomas Jefferson University in Philadelphia, say the new analysis shows that "men who have received previous DOC chemotherapy can be given radium-223 safely and its efficacy will be similar to patients who have not received previous DOC treatment."

But they also advocate caution. "The oncology community needs to proceed cautiously, since the ALSYMPCA trial was not able to identify the optimum sequence of administration of DOC and radium-223. Additionally, the trial was designed before the approval of enzalutamide (ENZ) and abiraterone acetate (AA), so the clinical bene-

(Continued on page 5)

DENDREON FILES FOR CHAPTER 11 AS PROVENGE DISAPPOINTS

Dendreon Corp. (DNDN), the maker of prostate-cancer drug Provenge®, filed for bankruptcy protection, potentially wiping out shareholders in a company that pioneered the use of patients' immune systems to fight tumors.

The agreement calls for a recapitalization of Dendreon, or a sale of the company or its assets, the Seattle-based drugmaker said in a statement. The company and its US subsidiaries filed Chapter 11 petitions in US Bankruptcy Court in Delaware.

Provenge, approved in 2010 as the first so-called immunotherapy, was designed to treat men with advanced-stage prostate cancer, the second-leading cause of cancer deaths among men in the US. The drug never lived up to expectations because it's cumbersome to administer and cost \$93,000. Treatment involves extracting white blood cells from a patient, mixing them with vaccine components and delivering the combination as an infusion.

Dendreon said it plans to continue operations during the restructuring and will provide Provenge to patients. The company has about 700 employees in Seattle and Bridgewater, New Jersey, after cutting about 750 full-time and contractor positions in 2012 and 2013.

The company, whose market value once topped \$7B, now has a market value of about \$29 million.

Bloomberg News, 10 November 2014

PROSTATE CANCER RECURRENCE RISK RISES WITH TRIGLYCERIDES

Elevated triglycerides after radical prostatectomy (RP) significantly increased the likelihood of prostate cancer recurrence, data from a study showed.

The risk of recurrence rose about 3% for every 10 mg/dL increase in triglycerides. Overall, other lipid parameters – total cholesterol, LDL, and HDL – did not have significant associations with prostate cancer recurrence. In the subgroup of men with dyslipidemia, however, higher total cholesterol levels were associated with an increased risk of recurrence, whereas higher HDL levels decreased the risk, as reported online in *Cancer Epidemiology, Biomarkers and Prevention*.

"These findings, coupled with evidence that statin use is associated with reduced recurrence risk, suggest that lipid levels should be explored as a modifiable risk factor for prostate cancer recurrence," Stephen J. Freedland, MD, of Duke University, and co-authors concluded.

Excess weight and obesity have a significant association with development of aggressive prostate cancer and prostate cancer mortality. Given the strong association between obesity and hypercholesterolemia, cholesterol has been postulated as a contributor to prostate cancer progression, the authors noted. Moreover, laboratory studies have suggested that cholesterol fuels prostate cancer growth by multiple signaling pathways.

(Continued on page 4)

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LONG-TERM COMPLICATIONS IN MEN WHO HAVE EARLY OR LATE RADIOTHERAPY AFTER RADICAL PROSTATECTOMY

Sowerby RJ, Gani J, Yim H, et al
Can Urol Assoc J 8:253–258, 2014

Introduction: Choosing adjuvant radiotherapy (RT) or salvage RT after radical prostatectomy (RP) for locally advanced prostate cancer is controversial. Performing RT early after RP may increase the risk of urinary complications compared to RT performed later. We evaluated the urinary complication rates of men treated with RP followed by early or late RT.

Methods: Using a retrospective chart review, we compared rates of urinary incontinence (UI), bladder neck contraction (BNC), or urethral stricture in men with prostate cancer treated with early RT (<6 months after RP) or late RT (≥6 months after RP), three years after RT.

Results: In total, 652 patients (between 2000 and 2007) underwent early RT (162, 24.8%) or late RT (490, 75.2%) after RP. The mean time to early RT was 3.6 months (range: 1-5 months) and to late RT was 30.1 months (range: 6-171 months). At three years post-RT, UI rates were similar in the early RT and the late RT groups (24.5% vs. 23.3%, respectively, $p = 0.79$). Prior to RT, 27/652 (4%) patients had a BNC and 11/652 (1.7%) had a urethral stricture, of which only one BNC persisted at three years post-RT. After RT, 17/652 (2.6%) BNC and 4/652 (0.6%) urethral stricture developed; of these, six BNC and two urethral strictures persisted at three years.

Conclusion: Rates of UI, BNC, and urethral stricture were similar with early and late RT at three years post-RT. These findings suggest that the timing of RT after RP does not alter the incidences of these urinary complications and can aid in the decision-making process regarding adjuvant RT versus salvage RT.

USE OF PDE5 INHIBITORS MAY ADVERSELY IMPACT BIOCHEMICAL RECURRENCE FOLLOWING RADICAL PROSTATECTOMY

Michl U, Molfenter F, Graefen M, et al
J Urol 4 September 2014; Epub

Purpose: Experimental evidence suggests that phosphodiesterase type 5 inhibitors (PDE5i) may suppress tumor growth, postpone metastasis, and prolong survival, but clinical data are lacking. We studied the effect of PDE5i on biochemical recurrence (BCR) after RP for prostate cancer.

Materials and Methods: The study comprised of 4,752 consecutive men with localized prostate cancer treated by bilateral nerve-sparing RP between January 2000 and December 2010. Of these, 1,110 (23.4%) men received PDE5i (PDE5i group) post-RP while 3,642 (76.6%) did not (non-PDE5i group). The risk of BCR was compared between the PDE5i and non-PDE5i groups. Cox multivariate proportional hazard models and confidence intervals were used to estimate the hazard ratio of BCR associated with PDE5i use. Propensity score-matched analysis was performed.

Results: Median follow-up was 60.3 months (IQR 36.7 - 84.5). Five-year BCR-free survival estimates in the PDE5i versus non-PDE5i patients were 84.7% (95% CI: 82.1% - 87.0%) and 89.2% (95% CI: 88.1 - 90.3%) ($p=0.0006$), respectively. Multivariate regression analysis showed that PDE5i use was an independent risk factor for BCR (HR: 1.38, CI: 1.11 - 1.70; $p=0.0035$). This was also true after propensity score matching.

Conclusions: Contrary to experimental data, use of PDE5i post-RP may adversely impact BCR following RP. Further studies are needed to validate our results.



DEXAMETHASONE MAY BEAT PREDNISOLONE IN CASTRATION RESISTANT PROSTATE CANCER

Daily dexamethasone (DEX) may be more effective than daily prednisolone (PRD) against castration-resistant prostate cancer (CRPC), as measured by PSA, according to a new phase 2 trial. The researchers say their study, published online on October 16 in *European Urology*, is the only completed randomized comparison of different corticosteroids in CRPC.

On intent-to-treat analysis, serum PSA responses were seen in 16 of 39 patients in the DEX arm, compared with just eight of 36 in the PRD arm (41% vs. 22%, p=0.08), according to Dr. Ramachandran Venkitaraman of Ipswich Hospital NHS and University Campus Suffolk in the UK and colleagues.

The results were slightly more pronounced in an analysis of men with at least two on-treatment PSA measurements at least one week apart, in whom the response rates were 47% (16 of 34) for DEX and 24% (eight of 33) for PRD (p=0.05). The report also highlighted that seven of 19 men (36%) who crossed over to DEX after PSA progression on PRD achieved a PSA response to DEX.

“Taken together with previous data on PRD and DEX in CRPC, our study challenges current clinical practice,” researchers write. “In the absence of more definitive trials, DEX should be used in preference to PRD.” They also suggest that, “Given that abiraterone, docetaxel, and cabazitaxel are approved for use in CRPC in combination with PRD, future studies should explore the use of DEX in combination with these agents.”

The primary study group consisted of 75 patients (median age 67), with 39 randomized to receive oral DEX 0.5 mg daily and 36 randomized to receive oral PRD 5 mg twice daily. (Initially, a third arm of seven patients had received intermittent DEX, but recruitment to this arm was stopped after none of the patients achieved a PSA response.)

The median time to PSA progression was 9.7 months for men in the DEX arm versus 5.1 months in the PRD arm. Of the 36 patients on PRD, 23 crossed over to DEX

(Continued on page 8)

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

“The Supplement Handbook” is the best book on supplements ever written! Okay I am a little biased here but I do believe you should pick up a copy ASAP!”

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

Bottom Line:

After working three years on it along with a full-time editor, the book (“The Supplement Handbook” from Rodale publishing – the same folks that do Men’s Health Magazine, Prevention etc.) is finally out now and available on Amazon, Barnes & Noble, iTunes, blah, blah, blah. It is about 500 pages with over 100 medical conditions including a section on prostate cancer and it answers all your other questions. Man, is this a shameless plug right before the holidays or what?!¹

I apologize but I have waited 30 years to find a book on every possible medical condition that could tell me what dietary supplements work and which ones are worthless. I am talking about supplements for prostate cancer, prostatitis, BPH, erectile dysfunction, hot flashes, bone health, weight loss... I have been writing for prostate newsletters for 15+ years as a volunteer and I have never been so shameless when plugging a book but I think you will love this one. This is all I really have to say this month! The book gives you all the lifestyle, diet, supplements and even drug tips on a variety of things. It will explain what you should look for when trying to figure out quality control issues

TESTOSTERONE THERAPY DOESN’T SEEM TO RAISE CANCER RISK IN MEN

The risk of developing cancer, including prostate cancer, is not elevated in men who receive long-term testosterone therapy, according to a new registry study.

“Some uncertainty remains about the safety of testosterone regarding prostate health,” lead author Dr. Michael L. Eisenberg from Stanford University School of Medicine in Stanford, California, told Reuters Health. “The current report demonstrated that with extensive follow-up there did not appear to be any increased risk of prostate cancer for men on testosterone.”

Several longitudinal studies have found no association between baseline testosterone levels and prostate carcinogenesis.

and there is even a chapter on how to analyze medical studies. From bone health to cancer to irritable bowel syndrome to osteoarthritis to depression to anxiety to celiac disease to whatever... it is all in there.

In addition, keep in mind that it is the holidays which not only means you can buy a copy for yourself but also for a friend and you will feel good knowing that you are supporting the Moyad Beer Fund. ALSO, AND PROBABLY MORE IMPORTANTLY, THE HOLIDAYS ARE THE TIME TO DONATE TO US TOO! This group is everywhere and always looking out for prostate cancer patients from advocacy to the latest information on clinical trials, and the information is free. However, they cannot continue to be so outstanding without continuous financial help from their readers! Please send them a donation this holiday season for whatever amount! This would also make my day!

Reference:

1. Moyad M. Sitting in his home office crossing his fingers that our football team just makes a bowl game this holiday season!

And an earlier meta-analysis of 19 placebo-controlled trials failed to show a higher risk of prostate cancer in men on testosterone therapy. But a short follow-up of these trials may have limited their ability to detect a long-term risk, Dr. Eisenberg and colleagues write in *BJU International*, online October 20.

The researchers linked 247 men treated with testosterone therapy over the past 20 years (and 211 untreated controls) with the Texas Cancer Registry to examine the association between cancer incidence (prostate and others) and testosterone therapy. Overall, 47 men developed cancer, including 8.1% of men on testos-

(Continued on page 5)

INTENSIVE ANDROGEN DEPRIVATION MAY HELP IN HIGH-RISK PROSTATE CANCER

Intensive neoadjuvant androgen deprivation therapy (ADT) prior to radical prostatectomy (RP) appears to reduce the tumor burden in men with localized high-risk prostate cancers (PCAs), according to a new phase 2 trial.

“Approximately 20 percent of newly diagnosed PCA patients have localized but high-risk disease; the cure rates for these men are suboptimal,” said Dr. Mary-ellen Taplin of Harvard Medical School in Boston, MA.

“My colleagues and I believe that limited but intense systemic therapy before or after surgery may increase the cure rate, but a large randomized, phase 3 trial is needed to prove a benefit,” she said.

Dr. Taplin and colleagues randomly assigned 58 men to 12 weeks of treatment with luteinizing hormone-releasing hormone agonist (LHRHa; leuprolide acetate) alone or with abiraterone acetate (AA). After a prostate biopsy, all men received 12 additional weeks of LHRHa plus AA followed by RP.

The levels of intraprostatic androgens from 12-week prostate biopsies were significantly lower with LHRHa plus AA compared with LHRHa alone, the researchers report in the *Journal of Clinical Oncology*, online October 13th. “A subset of patients in our trial had dramatic shrinkage of tumor and the remainder had modest responses,” Dr. Taplin noted.

“Laboratory analyses are underway to help us understand the mechanisms of response and resistance in these tumors,” she added. “The laboratory analyses from this trial will help strategize combinations of drugs and treatment duration and provide the groundwork for development of larger trials in this area.”

In a linked editorial, Dr. Eric J. Small of the University of California, San Francisco, cautions that “It is important to note that this study was not designed to test the clinical benefit of this approach, nor was it powered to detect differences in clinical or pathologic outcomes.”

Still, he concluded that the paper is “an important contribution” toward answering the many questions related to targeting of the androgen receptors.

Reuters Health, 29 October 2014

TRIGLYCERIDES AND RISK OF RECURRENCE *(Continued from page 1)*

“Although epidemiologic evidence does not support an association between serum cholesterol levels and risk of total prostate cancer, there is a suggestion that elevated cholesterol may be associated with increased risk of aggressive disease, although not all studies have reported this finding,” said Freedland and co-authors.

The pervasiveness of overweight, obesity, and elevated cholesterol in Western societies has provided a rationale for studies to clarify cholesterol’s association with prostate cancer. To address the issue, Freedland and colleagues queried the Shared Equal Access Regional Cancer Hospital (SEARCH) database to identify prostate cancer patients who had no history of statin use prior to RP during 1999 through 2013.

The search initially identified 2,542 men who underwent RP at six Veterans Affairs hospitals in California, North Carolina, and Georgia. Investigators excluded 1,135 men who had a history of statin use prior to surgery, 482 who did not have preoperative lipid values, and 83 others because of missing data, leaving 843 men for inclusion in the analysis.

For purposes of the study, the authors chose cutoff values for normal versus abnormal lipid parameters consistent with the National Cholesterol Education Program Adult Treatment Panel: 200 mg/dL for total cholesterol, 130 mg/dL for LDL, 40 mg/dL for HDL, and 150 mg/dL for triglycerides. Each patient was classified as having normal or abnormal values for each lipid parameter, meaning that a patient might have normal levels of one parameter but abnormal values for others.

The data showed that 325 men had abnormal cholesterol levels prior to RP. These men were more likely to begin statin treatment after surgery as compared with men who had normal preoperative cholesterol levels ($P < 0.001$). Otherwise, men with normal or abnormal preoperative lipid values did not differ significantly.

During a median follow-up of 74.4 months, 293 men had biochemical recurrence (BCR) of prostate cancer. Kaplan-Meier plots showed no significant association between total cholesterol and the risk of BCR ($P = 0.334$), a finding that was confirmed by multivariable analyses ($P \geq 0.4$). Analyses of HDL and LDL yielded

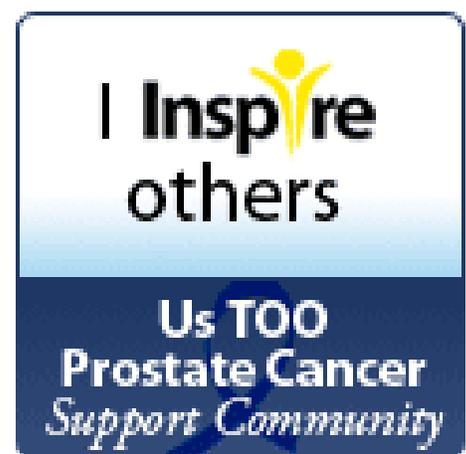
similar results for those two lipid parameters. Elevated triglyceride levels were associated with a 35% increase in the hazard for BCR (HR 1.35, 95% CI 1.05-1.74). Given the association of hypertriglyceridemia and diabetes, investigators repeated the analyses after excluding men with diabetes, and a stronger association emerged for elevated triglycerides and BCR (HR 1.46, 95% CI 1.10-1.93).

Freedland and colleagues performed more detailed analyses of the relationship of BCR to total cholesterol, LDL, and HDL. Preliminary findings suggested an association among men who had abnormal lipid values at baseline. Repeating the analyses only in patients who had abnormal baseline lipid values, the investigators found significant associations with total cholesterol and HDL.

The risk of BCR increased by 9% (CI 1.01-1.17) with each 10 mg/dL increase in total cholesterol above 200 mg/dL. The risk of recurrence declined by 39% (CI 0.41-0.91) for every 10 mg/dL rise in HDL. The authors found no significant interactions between abnormal lipid values and postoperative statin use.

“Although the association between obesity and increased risk of prostate cancer recurrence is likely to be multifactorial, these findings suggest that dyslipidemia may be one of the mechanisms underlying this association,” the authors said of their study.

MedPage Today, 10 October 2014



www.inspire.com

SEQUENCING RADIUM-223 AND DOCETAXEL *(Continued from page 1)*

fit of concomitant or sequential use of radium-223 with these drugs is unknown. Perhaps most intriguing would be the opportunity to integrate immunotherapy.”

Dr. Kelly indicated that the design of the ALSYMCA study was insightful because analyzing clinical outcomes on the basis of previous DOC use was not done in a post hoc manner, but was prespecified. “They were mindful of the significance of DOC for these patients,” he said.

“Until recently, DOC was the only option available for men with mCRPC. That is why the data suggesting clinical benefits with or without previous DOC is welcome news,” he said. However, there are now two other therapeutic options that can be used instead of chemotherapy in mCRPC – AA (Zytiga®), approved for first-line use in December 2012, and ENZ (Xtandi®), approved for first-line use in September. At present, it is unclear where radium-223 fits in with the use of these two therapies, although there are clinical trials underway to address this.

The subset analysis of the phase 3 ALSYMCA study was reported by Peter Hoskin, MD, from the Mount Vernon Cancer Centre in Northwood, Middlesex, UK, and colleagues. Median overall survival with radium-223 was 14.4 months for men who received previous DOC and 16.1 months for men who did not. Correspondingly, median time to first symptomatic skeletal event was 13.5 months and 17.0 months, respectively, for the two groups. Compared with placebo, hazard ratios for the two groups of men were 0.70 and 0.69, respectively, and both were statistically significant.

Dr. Hoskin and colleagues also report that men who had prior DOC treatment had a higher incidence of hematologic toxicities of any grade, and 62% of men previously treated with DOC had grade 3/4 adverse events, compared with 54% without DOC. Men who had previously been treated with DOC had a higher incidence of grade 3/4 thrombocytopenia with radium-223 than with placebo (9% vs. 3%), whereas the incidence was similar between treatment groups among men with no previous DOC use (3% vs. 1%).

The incidences of grade 3/4 anemia and neutropenia were similar with radium-

223 and placebo within both DOC subgroups, and non-hematologic toxicities were similar in the two groups.

In their discussion, Dr. Hoskin and colleagues state: “Extensive use of previous DOC (e.g., more than 6 cycles) might contribute to adverse effects with radium-223; however, this possibility cannot be investigated, since cumulative DOC dosing data were not collected in this trial.”

“This is an important point when sequencing two drugs,” said Dr. Kelly. The optimum sequence for administering both drugs was not answered by this study, according to Dr. Kelly. “In current clinical practice, knowing the optimum sequence would be important to optimize the clinical benefit and limit the toxicities from therapies,” he said.

“In the comment, a question was raised as to how radium-223 can be integrated into immunotherapy. Radium-223 is an ideal agent to combine with immunotherapy, and might induce an immunologic response similar to the abscopal effect,” Dr. Kelly said. “An abscopal effect is a phenomenon where local radiotherapy can induce systemic immunologic response and cause tumor regression at distal sites,” he explained.

However, this speculation needs to be backed-up with data from clinical studies. Currently, novel immunotherapies such as ipilimumab (Yervoy®) have not shown clinical benefit to date in mCRPC. A recent study with local radiotherapy with or without ipilimumab after DOC did not meet the primary end point of overall survival for men with mCRPC.

Is combination therapy better than sequencing two agents? Dr. Kelly indicated that combining DOC plus other agents has failed in many clinical studies. But clinicians are still hopeful other combinations will fare better.

Dr. Hoskin and colleagues report that a phase 1/2 trial is ongoing to determine whether DOC and radium-223 are effective for men with mCRPC and bone metastases. In addition, the ERA 223 trial is enrolling men with mCRPC with bone metastases to determine if radium-223 and AA will be more effective than AA and placebo.

Medscape Medical News, 24 October 2014

TESTOSTERONE THERAPY

(Continued from page 3)

terone therapy and 12.8% of men not on testosterone therapy ($p=0.1$), the team found.

These rates were higher than expected for the general Texas population, and the excess risk seemed to be explained entirely by a threefold higher-than-expected number of prostate cancer cases. Neither the overall cancer incidence (hazard ratio, 1.0) nor the prostate cancer risk (HR, 1.2) differed significantly by treatment group. And there was no significant difference in the prostate biopsy rates between men who did and did not take testosterone (25.9% vs. 31.8%, $p=0.17$).

What did seem to contribute to prostate cancer risk, though, was the baseline PSA level. Men below the median 1.1 ng/mL had no altered risk of prostate cancer regardless of testosterone therapy, whereas men above the median had a prostate cancer risk 3.51 times higher, also regardless of testosterone therapy.

“I think providers should be mindful of the fact that prostate cancer risk varies with PSA level,” Dr. Eisenberg said. “But our data did not demonstrate that testosterone changed that risk, just that a higher PSA makes it more likely for a man to be diagnosed (whether or not he’s on testosterone).”

“As we continue to evaluate the risks of and benefits of testosterone supplementation therapy, it’s important to have a balanced view not only of the harms but also of the lack of harms caused by these treatments,” he concluded.

Reuters Health, 30 October 2014



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MR-GUIDED PROSTATE BIOPSY FOR PLANNING OF FOCAL SALVAGE FOR BIOCHEMICAL FAILURE AFTER RADIATION

Ménard C, Iupati D, Publicover J, et al

Radiology 8 September 2014; Epub

Purpose: To determine if the integration of diagnostic magnetic resonance (MR) imaging and MR-guided biopsy would improve target delineation for focal salvage therapy in men with prostate cancer.

Materials and Methods: Between September 2008 and March 2011, 30 men with biochemical failure after radiation therapy for prostate cancer provided written informed consent and were enrolled in a prospective clinical trial approved by the institutional research ethics board. An integrated diagnostic MR imaging and interventional biopsy procedure was performed with a 1.5-T MR imager by using a prototype table and stereotactic transperineal template. Multiparametric MR imaging (T2-weighted, dynamic contrast material-enhanced, and diffusion-weighted sequences) was followed by targeted biopsy of suspicious regions and systematic sextant sampling. Biopsy needle locations were imaged and registered to diagnostic images. Two observers blinded to clinical data and the results of prior imaging studies delineated tumor boundaries. Area under the receiver operating characteristic curve (Az) was calculated based on generalized linear models by using biopsy as the reference standard to distinguish benign from malignant lesions.

Results: Twenty-eight patients were analyzed. Most patients (n = 22) had local recurrence, with 82% (18 of 22) having unifocal disease. When multiparametric volumes from two observers were combined, it increased the apparent overall tumor volume by 30%; however, volumes remained small (mean, 2.9 mL; range, 0.5-8.3 mL). Tumor target boundaries differed between T2-weighted, dynamic contrast-enhanced, and diffusion-weighted sequences (mean Dice coefficient, 0.13-0.35). Diagnostic accuracy in the identification of tumors improved with a multiparametric approach versus a strictly T2-weighted or dynamic contrast-enhanced approach through an improvement in sensitivity (observer 1, 0.65 vs.

(Continued on page 8)

MORE PROSTATE CANCER DEATHS WITH RADIATION THAN SURGERY

External beam radiation therapy (EBRT) is associated with higher prostate cancer-specific mortality (PCSM) than is radical prostatectomy (RP), even at similar treatment-based predicted progression-free probabilities, new research shows.

“Patients with a biochemical recurrence (BCR) after EBRT have a higher risk of prostate cancer mortality compared with patients with a BCR after surgery,” study co-author Dr. Jay P. Ciezki from the Cleveland Clinic in Ohio stated.

But he cautioned that the survival differences between the two treatment groups were small so it should not enter into the decision-making algorithm at this point.

“We believe that the focus should be on how to manage BCR. Pre-existing data suggest that BCR alone is not a reason to treat; rather that symptoms or evidence on an image (CT, MRI, bone scan, etc.) are more appropriate reasons to initiate treatment. Our study does not change this dictum,” he said.

Co-author Chandana Reddy, a biostatistician at the Cleveland Clinic, added in an email, “This study shows that BCR outcomes are not a proxy for prostate cancer-specific mortality. It may not be appropriate to make comparisons among treatment modalities using BCR.”

The authors studied more than 13,800 men who underwent RP (n=8,308), EBRT (n=2,839), or brachytherapy (n=2,656) over about 18 years at two academic medical centers in the U.S. The findings were published online October 5 in *European Urology*. The team calculated the five-year progression-free probability (5Y-PFP) for each patient based on the treatment received, using a treatment-specific nomogram to predict BCR.

Men treated with EBRT had higher 10-year PCSM compared with those having RP, across the range of nomogram-predicted risks of BCR. Ten-year PCSM rates with RT vs. RP were 3% vs. 0.9% when 5Y-PFP was >75%; 6.8% vs. 5.9% when 5Y-PFP was 51-75%; 12.2% vs. 10.6% when 5Y-PFP was 26-50%; and 26.6% vs. 21.2% when 5Y-PFP was 25% or lower.

After adjusting for nomogram-predicted 5Y-PFP, EBRT was linked with significantly increased PCSM compared with

RP (hazard ratio, 1.5; p=0.006). The authors found no significant difference in PCSM between patients treated with brachytherapy and RP, but they say patient-selection factors and lack of statistical power limited their analysis.

“This difference in risk of prostate cancer mortality may be attributed to: 1) differences in the definition of BCR, allowing for earlier detection of BCR in surgery patients; 2) earlier implementation of salvage therapy after a BCR in the surgery population; 3) the ability to deliver a more effective salvage therapy for surgery patients (i.e. EBRT); 4) radiation doses delivered by EBRT, which may be less effective in ablating cancer within the prostate,” Dr. Ciezki said.

Reddy explained, “The ways BCR is defined after surgery vs. radiation are very different. Because the surgery definition is based on a PSA value (0.4 ng/mL), BCR after surgery can be detected much sooner than BCR after radiation, which is based on a pattern of PSA values.” This study suggests that the BCR definition used for patients treated with EBRT may need to be modified in order to better predict the risk of prostate cancer mortality after BCR.

Dr. Frank Chinegwundoh, a urological surgeon at Barts Health National Health Service Trust in London, questioned the study’s value. “What the man in the street wants to know is which treatment – surgery, EBRT, and brachytherapy – will enable him to live longer,” he stated. “This study does not answer that. It is not comparing things in a randomized controlled clinical trial. Also, the patients having external RT are older, less fit, with worse disease.”

Reddy countered that such a trial will never be done. “Many attempts have been made, but none has been successful due to patients’ unwillingness to be randomized to such very different treatments,” she said. “In the absence of randomized trials, data from large registries is the best information we have to examine outcomes after prostate cancer treatment. This study did take into account differences in disease severity among the treatment groups.”

Reuters Health, 30 October 2014

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/>

a1p1c1 Men with mCRPC now have four treatment options prior to docetaxel (DOC) chemotherapy: abiraterone acetate (AA), enzalutamide (ENZ), Provenge®, and radium-223. The optimal sequencing order has yet to be determined; however, the recent randomized trial of androgen deprivation therapy (ADT) vs. ADT plus DOC may complicate this sequencing challenge because it could result in most men with metastatic disease receiving chemotherapy before having an opportunity to receive the other newer therapies. Studies with ENZ and AA have shown that both improve survival regardless of giving them before or after DOC. Now the study by Hoskin et al also shows a similar effect for radium-223. The only downside, however, is the higher morbidity when radium-223 was given after chemotherapy. More work is still needed to figure out the best sequencing strategy because the ADT + DOC study was undertaken before AA and ENZ were available. That means more work is needed to determine if men still are better off getting the DOC when ADT is begun rather than waiting until all the other options have been tried first.

The Bottom Line: Radium-223 is effective in men before or after DOC, but it is better tolerated in men who have not yet received chemotherapy.

a4p2c2 Many men use PDE5 inhibitors after radical prostatectomy (RP) to improve sexual function. Few have questioned if there could be any negative effect on cancer recurrence. In fact, some have suggested that it might improve outcome. Now Michl et al provide some interesting data. They conducted a retrospective analysis of men to determine the odds of a biochemical recurrence (BCR) after taking one of these drugs. Surprisingly, men were more likely to get recurrent disease if they took one of these drugs after RP. No explanation is given to help understand the mechanism for this effect. Also, the study design does not permit a definitive conclusion. It did not provide information on the duration of therapy, whether it was consistent across all PDE5 inhibitor drugs, or whether the dosage mattered. Therefore, the findings are not definitive. However, they do raise a red flag that necessitates doing a properly controlled study sooner rather than later.

The Bottom Line: Further studies are needed to determine if PDE5 inhibitors increase the risk of a BCR after RP.

a5p2c3 One of the concerns about radiation therapy (RT) after RP is the risk of complications such as incontinence, bladder neck contracture, or urethral stricture. That is one reason some clinicians choose not to use it early despite a randomized study showing a small benefit. The study by Sowerby et al provides some interesting data about the incidence of side effects with early or late RT. Their findings show no significant difference in any of these side effects. As is often the case, limitations in the study make the results uncertain. For example, they did not provide data about the method of RT or the dose administered, which are likely to have varied considerably. Another issue is determining what measurements were used to define the side effects. Did men complete validated surveys to assess incontinence? Also, what proportion received ADT and did it impact the results? Lastly, the study did not measure impotence or bowel side effects.

The Bottom Line: More information is needed to know if men who receive early RT after RP are at increased risk of complications compared to delayed RT.

a6p3c1 Is there an optimal steroid that should be used in men with CRPC? Venkitaraman, et al addressed that question in a small, phase II trial. They compared prednisolone (PRD) to dexamethasone (DEX) and found better results with the latter drug. However, one limitation is that they based their assessment only on PSA, not objective parameters. As often stated here, PSA is still not accepted as a valid end point for studies of men with advanced disease. Also, the study is small and it is unclear what other treatments the men in each group received both before and after entering this study. Although the authors conclude that DEX should be the preferred drug of choice based on their study that is not a valid conclusion. Changing practice requires well-done studies that clearly prove an alternative treatment is better and this study does not do that.

The Bottom Line: For now, PRD is a reasonable drug to use in men with

CRPC; however, further studies using DXM are worth doing.

a8p3c2 On billboards, radio, and TV, men are being bombarded with advertisements for testosterone therapy (TT). The FDA is now looking into whether some of the marketing has gone beyond the approval given for this treatment. Among the concerns is the possibility that it might increase a man's risk of developing prostate cancer. A small retrospective study by Eisenberg et al provides some comfort about this risk. They found no difference in incidence of prostate cancer among a group of men taking TT as compared to a control group not getting the drug. Unfortunately, this study raises several questions. Some of the problems are (1) whether both groups had similar patterns of PSA testing, (2) whether a PSA was managed similarly meaning what PSA warranted a biopsy, (3) how similar were the groups in terms of having high-risk patients with a greater likelihood for the disease, and (4) how the groups compared in terms of biopsy methods (i.e. did they have MRI-guided biopsies or how many needle cores were obtained). Without a prospective study, the long-term risk of TT cannot truly be determined.

The Bottom Line: The long-term risk of TT causing prostate cancer still needs further investigation.

a9p4c1 Could high-risk patients benefit from ADT prior to RP? Taplin and co-workers addressed that question by comparing ADT alone to ADT plus AA in men scheduled for RP. The patients all received treatment for 12 weeks, had a prostate biopsy and then received another 12 weeks of treatment. They found some patients had a dramatic decrease in tumor size. Dr. Small correctly pointed out that this treatment was not designed to demonstrate a clinical benefit so it remains unclear whether this treatment has value. However, this question has partly been addressed previously. Six randomized studies were conducted to assess the value of pre-surgical ADT and all of them were negative. Whether adding AA to ADT will change those results remains unclear but only a carefully controlled prospective study can make that determination.

(Continued on page 8)

THE BOTTOM LINE

(Continued from page 7)

The Bottom Line: At this time, there is no proof that men with high-risk disease should have aggressive ADT prior to undergoing a RP.

a10p6c1 Is focal therapy in men with local recurrence feasible? The answer will depend in part on the ability to properly identify the region(s) of recurrent disease. Menard et al conducted a small, prospective study using multiparametric imaging and targeted biopsies. Although diagnostic accuracy was better with the multiparametric rather than with the T2 weighted approach, the sensitivity was not very high. In addition, there will be a long road ahead to determine if men would benefit from targeted focal therapy. Assessing the impact will require more than demonstrating recurrent tumor can be identified and treated. It will be necessary to show that survival is improved or disease related morbidity could be reduced.

The Bottom Line: Identifying local recurrence after RT may be possible with targeted biopsies and MRI, however, the value of that approach needs to be determined by long-term prospective studies.

DEXAMETHASONE

(Continued from page 3)

following biochemical disease progression. Clinically significant toxicities were uncommon in both treatment arms, and no significant differences were seen between the two arms in terms of safety and tolerability.

Limitations included the study’s small size, an inability to gain any insight into how DEX might be more active against CRPC than PRD and the lack of crossover to PRD after disease progression on DEX. The authors also noted that they could not exclude the possibility that DEX activity following disease progression on PRD represented a withdrawal response to stopping PRD.

Although it’s possible that DEX could be more effective than PRD when combined with other anticancer drugs, such an option “cannot be recommended on current data,” stated Dr. Chris Marsden of the Royal Marsden Hospital in Sutton, Surrey, UK, who was not involved in the study.

Reuters Health, 3 November 2014

MR-GUIDED BIOPSY

(Continued from page 6)

0.35 and 0.44, respectively; observer 2, 0.82 vs. 0.64 and 0.53, respectively; P <0.05) and improved further with a 5-mm expansion margin (Az = 0.85 vs. 0.91 for observer 2). After excluding three patients with fewer than six informative biopsy cores and six patients with inadequately stained margins, MR-guided biopsy enabled more accurate delineation of the tumor target volume by means of exclusion of false-positive results in 26% (five of 19 patients), false-negative results in 11% (two of 19 patients) and by guiding extension of tumor boundaries in 16% (three of 19 patients).

Conclusion: The integration of guided biopsy with diagnostic MR imaging is feasible and alters delineation of the tumor target boundary in a substantial proportion of patients considering focal salvage.

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